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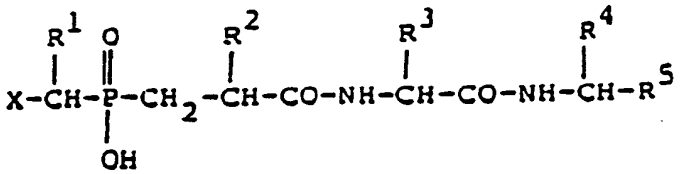
(54) Phosphinic acid derivatives.

(57) The invention provides compounds of the formula



I

wherein R^1-R^5 and X have the significance given in the description, and their pharmaceutically acceptable salts. They inhibit the enzyme collagenase and can be used in the form of medicaments for the control or prevention of degenerative joint diseases such as rheumatoid arthritis and osteoarthritis. The compounds of formula I and their pharmaceutically acceptable salts can be manufactured according to generally known methods.

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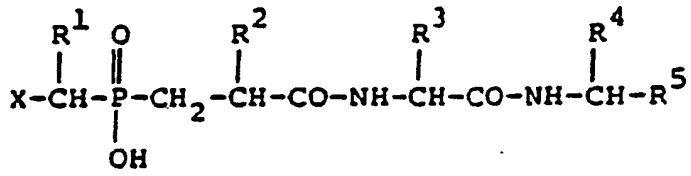
Phosphinic Acid Derivatives

The present invention is concerned with phosphinic acid derivatives, a process for the manufacture thereof and medicaments containing said derivatives.

The phosphinic acid derivatives provided by the present invention are compounds of the general formula



I

wherein

R^1 represents a hydrogen atom or a C_1-C_6-alkyl or aryl-(C_1-C_6-alkyl) group;

R^2 represents a C_2-C_5-alkyl group;

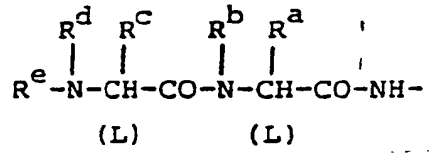
R^3 represents the side-chain of a natural α-amino acid in which any functional group present is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, with the proviso that R^3 does not represent a hydrogen atom or a methyl group;

R^4 represents a hydrogen atom or a methyl group; or

R^3 and R^4 together represent a group of the formula $-(CH_2)_n-$ in which n stands for a number from 4 to 11 inclusive;

R^5 represents a hydrogen atom or a C_1-C_6-alkyl, carboxyl, C_1-C_6-alkoxycarbonyl or C_1-C_6-alkylaminocarbonyl group; and

X represents either a cyclic imido group derived from an aliphatic or aromatic dicarboxylic acid, from an N-carboxyamino acid, from an azadicarboxylic acid or from an O-carboxyhydroxy acid or a group of the formula



(a)

in which R^a represents the side-chain of a natural α-amino acid in which any functional group present is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, R^b represents a hydrogen atom or R^a and R^b together represent a trimethylene group, R^c represents the side-chain of a natural α-amino acid in which any functional group is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, R^d represents a hydrogen atom or R^c and R^d together represent a trimethylene group and Rf^e represents a protecting group or an acyl, C_1-C_6-alkyl-sulphonyl or arylsulphonyl group.

and pharmaceutically acceptable salts thereof.

As used herein, the term "C_1-C_6-alkyl", alone or in combinations, means a straight-chain or branched-chain alkyl group containing from 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl etc. The term "C_2-C_5-alkyl" means a straight-chain or branched-chain alkyl group containing from 2 to 5 carbon atoms. The term "C_1-C_6-alkoxy", alone or in combination, means an alkoxy group containing from 1 to 6 carbon atoms, examples of C_1-C_6-alkoxy groups being methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy etc. The term "acyl" means an acyl group derived from an aliphatic carboxylic acid (e.g. a C_1-C_6-alkanoic acid such as acetic acid, propionic acid, butyric acid etc), from an aromatic carboxylic acid (e.g. benzoic acid or a benzoic acid which is substituted by one or more substitutents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, carboxy, halogen, trifluoromethyl, etc.) or from an araliphatic carboxylic acid [e.g., an aryl-(C_1-C_6-alkanoic)acid such as phenylacetic acid, etc]. The term "aryl", alone or in combinations, means a phenyl group which is optionally substituted with one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl,

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etc. The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "side-chain of a natural α-amino acid" means the group R in an α-amino acid of the formula H_2N-CH(R)-COOH which is naturally occurring. Thus, subject to the proviso with respect to R^3, the side-chain can be, for example, one of the following, with the corresponding α-amino acid being indicated thereafter in parenthesis: hydrogen (glycine), methyl (alanine), isopropyl (valine), isobutyl (leucine), benzyl (phenylalanine), p-hydroxybenzyl (tyrosine), hydroxymethyl (serine), mercaptomethyl (cysteine), 1-hydroxyethyl (threonine), 2-methylthioethyl (methionine), carboxymethyl (aspartic acid), 2-carboxyethyl (glutamic acid), 3-guanidinopropyl (arginine) or 4-aminobutyl (lysine).

Any functional group present in R^a, R^c and R^3 can be protected in a manner which is known per se in peptide chemistry. For example, a hydroxy group can be protected in the form of a readily cleavable ether such as the tert-butyl, benzyl or tetrahydropyranyl ether or in the form of a readily cleavable ester such as the acetate. A mercapto group can be protected, for example, by a tert-butyl, benzyl or like group. An amino group can be protected, for example, by a tert.butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, trifluoroacetyl, 2-(bi-phenylyl)-isopropoxycarbonyl or isobornyloxycarbonyl group or in the form of a phthalimido or like group. A carboxy group can be protected, for example, in the form of a readily cleavable ester such as the methyl, ethyl, tert.butyl, benzyl or like ester.

An amino group present in R^a, R^c and/or R^3 can be acylated with an acyl group as defined earlier or with an aminocarboxylic acid. Examples of such aminocarboxylic acids are α-amino acids such as the natural α-amino acids (e.g. glycine, alanine, etc). Alternatively, an amino group present in R^a, R^c and/or R^3 can be sulphonylated with, for example, a C_1-C_6-alkanesulphonic acid (e.g. methanesulphonic acid) or an arylsulphonic acid (e.g. benzenesulphonic acid or p-toluenesulphonic acid).

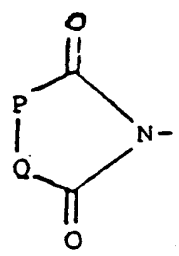
A carboxyl group present in R^a, R^c and/or R^3 can be amidated in a conventional manner. Thus, examples of amidated carboxyl groups are the aminocarbonyl, (C_1-C_6-alkyl)aminocarbonyl, di(C_1-C_6-alkyl)-aminocarbonyl or arylaminocarbonyl groups as well as a carboxyl group amidated with an aminocarboxylic acid such as a natural α-amino acid (e.g. glycine, alanine etc).

When R^e in a group of formula (a) represents a protecting group, this can be any amino protecting group which is known per se in peptide chemistry (e.g. the amino protecting groups mentioned earlier).

The compounds of formula I form pharmaceutically acceptable salts with bases such as alkali metal hyroxides (e.g. sodium and potassium hydroxide), alkaline earth metal hydroxides (e.g. calcium hydroxide and magnesium hydroxide), ammonium hydroxide, etc. The compounds of formula I which are basic form pharmaceutically acceptable salts with acids. As such salts there come into consideration not only salts with inorganic acids such as hydrohalic acids (e.g. hydrochloric acid and hydrobromic acid), sulphuric acid, nitric acid, phosphoric acid, etc, but also salts with organic acids such as acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulphonic acid, p-toluenesulphonic acid, etc.

The compounds of formula I contain at least two asymmetric carbon atoms and can accordingly exist as optically active enantiomers, as diastereoisomers or as racemates.

In formula I above R^1 preferably represents a hydrogen atom or a C_1-C_6-alkyl group, especially a hydrogen atom or a methyl group. R^2 preferably represents a C_3-or C_4-alkyl group, especially a n-propyl, isobutyl or sec.butyl group. Preferably, R^3 represents an isobutyl group and R^4 represents a hydrogen atom or R^3 and R^4 together represent a group of the formula -$(CH_2)_n$-in which n stands for a number from 5 to 9 inclusive and R^5 represents a hydrogen atom or R^3 represents an isobutyl group, R^4 represents a methyl group and R^5 represents a carboxyl or C_1-C_6-alkoxycarbonyl group, especially a carboxyl or ethoxycarbonyl group. When X represents a cyclic amido group, in one preferred embodiment this is a group of the formula



(b)

wherein P and Q together represent a group of the formula -CH(R^f)-CH(R^f)-,
-CH(R^f)-CH(R^f)-CH(R^f)-,
-O-CH(R^f)-,

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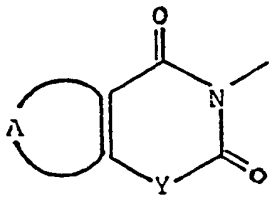
$-N(R^f)-CH(R^f)-$,
$-N(R^f)-N(R^f)-$,
$-N=N-$ or
$-C(R^f)=C(R^f)-$,

in which each R^f represents a hydrogen atom or a C_1-C_6-alkyl, aryl, aryl-(C_1-C_6-alkyl), C_1-C_6-alkanoylamino group or an acylamino group in which the acyl moiety is derived from a naturally occurring α-amino acid in which the amino group is optionally protected,
or P and Q together represent an optionally substituted aromatic system in which the optional substitution comprises one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, hydroxy, aryl-(C_1-C_6-alkoxy), nitro, amino, C_1-C_6-alkanoylamino, mono(C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino and C_1-C_6-alkylsulphonylamino. In another preferred embodiment the cyclic imide X is a group of the formula



(c)

wherein A represents the residue of an optionally substituted aromatic system in which the optional substitution comprises one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, hydroxy, aryl-(C_1-C_6-alkoxy), nitro, amino, C_1-C_6-alkanoylamino, mono(C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino and C_1-C_6-alkylsulphonylamino and Y represents -O-, -NH-or $-NR^g$-in which R^g represents hydrogen or C_1-C_6-alkyl.

The optionally substituted aromatic system denoted by P and Q together in formula (b) can be monocyclic (e.g. 1,2-phenylene or thienylene) or polycyclic (e.g. 1,2-naphthylene, 2,3-naphthylene, 1,8-naphthylene, 2,3-anthrylene, etc). The symbol A in formula (c) can represent the residue of an optionally substituted monocyclic aromatic system (e.g. benzene) or an optionally substituted polycyclic ring system (e.g. naphthalene, anthracene, etc).

In a particularly preferred embodiment the cyclic imide group X is a group of formula (b) wherein P and Q together represent a group of the formula $-C(R^f)=C(R^f)-$ in which one R^f represents an aryl group, especially a phenyl group, and the other R^frepresents a hydrogen atom or an aryl group, especially phenyl group. In another particularly preferred embodiment the cyclic amido group X is a group of formula (b) wherein P and Q together represent a 1,2-phenylene or 2,3-naphthylene group which is optionally substituted by one or more substituents selected from C_1-C_6-alkoxy, halogen, hydroxy, amino and C_1-C_6-alkanoylamino. In yet another particularly preferred embodiment the cyclic imide group X is a group of formula (b) wherein P and Q together represent a 1,8-naphthylene group which is optionally substituted by one or more substituents selected from C_1-C_6-alkoxy, halogen, hydroxy, amino and C_1-C_6-alkanoylamino. In a further particularly preferred embodiment, the cyclic imido group X is a group of formula (c) in which A represents the residue of a benzene ring and Y represents $-NR^g$-.

When X represents a group of formula (a) above, preferably R^a represents the side-chain of a natural α-amino acid in which any functional group present is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, especially an isobutyl group, and R^b represents a hydrogen atom, R^c and R^dtogether represent a trimethylene group and R^e represents a protecting group, especially a benzyloxycarbonyl group, or an acyl group, especially an acetyl group.

Particularly preferred compounds of formula I hereinbefore are:
[(3-aminophthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid,
[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid,
[(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid,
N-[N-[(R or S)-2-[[[[[N-[1-(benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl]hydroxyphosphinyl]methyl]-4-methylvaleryl]-L-leucyl]-L-alanine and
[[1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl]methyl][[(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]-carbamoyl]pentyl]phosphinic acid.

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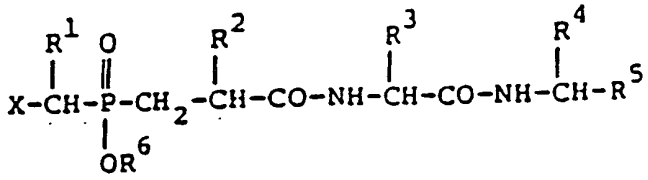
According to the process provided by the present invention, the compounds of formula I above and their phamaceutically acceptable salts are manufactured by treating a compound of the general formula



II

wherein R^1,R^2,R^3,R^4,R^5 and X have the significance given above and R^6 represents a C_1-C_6-alkyl group, with an acid or with a halotrimethylsilane, if desired functionally modifying a reactive substituent present on a cyclic imide group denoted by X in a compound of formula I obtained and, also if desired, converting a compound of formula I obtained into a pharmaceutically acceptable salt.

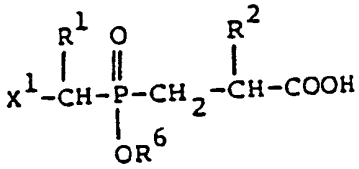
The treatment of a compound of formula II, preferably one in which R^6 represents methyl or ethyl, with an acid or with a halotrimethylsilane can be carried out in a manner known per se. Thus, for example, a compound of formula II can be treated with hydrogen bromide in acetic acid at about room temperature or with trifluoroacetic acid in an inert organic solvent (e.g. a halogenated hydrocarbon such as dichloromethane etc) at about room temperature. Again, for example, a compound of formula II can be treated with a halotrialkylsilane, preferably bromotrimethylsilane, in an inert organic solvent, (e.g. a halogenated hydrocarbon such as dichloromethane etc) at about room temperature.

A reactive substituent which is present on a cyclic imido group denoted by X in a compound of formula I can be functionally modified if desired. Thus, for example, a nitro group can be reduced to an amino group in a known manner, for example by hydrogenation in the presence of a catalyst such as a palladium catalyst. Again, for example, an aryl-(C_1-C_6-alkoxy) group such as benzyloxy can be converted into a hydroxy group in a known manner, for example by hydrogenation in the presence of a catalyst such as a palladium catalyst. Further, for example, an activated aromatic hydrogen atom can be replaced by a halogen atom by halogenation in a known manner.

A compound of formula I obtained can be converted into a pharmaceutically acceptable salt in accordance with known methods. Thus, a compound of formula I can be converted into a pharmaceutically acceptable salt by treatment with a base such as one of the bases mentioned earlier. A compound of formula I which is basic can be converted into a pharmaceutically acceptable acid addition salt by treatment with an acid such as one of the acids mentioned earlier.

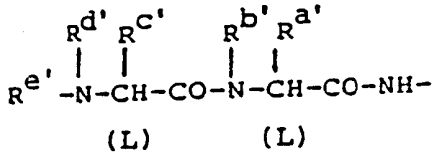
The compounds of formula II which are used as starting materials in the process provided by the present invention are novel and also form a object of the present invention.

The compounds of formula II can be prepared, for example, by condensing a compound of the general formula



III

wherein R^1, R^2 and R^6 have the significance given earlier and X^1 represents either a cyclic imido group as defined earlier or a group of the formula



(a')

wherein $R^{a'}$ represents the side-chain of a natural α-amino acid in which any functional group present is protected and $R^{b'}$ represents a hydrogen atom or $R^{a'}$ and $R^{b'}$ together represent a trimethylene group, $R^{c'}$ represents the side-chain of a natural α-amino acid in which any functional group present is protected and

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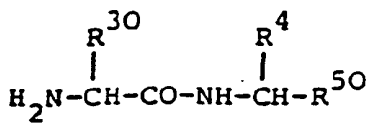
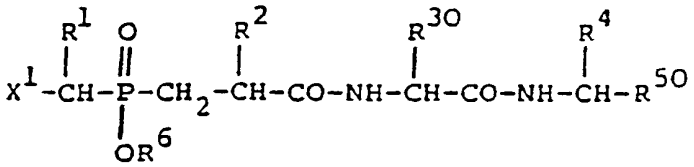
$R^{d'}$ represents a hydrogen atom or $R^{c'}$ and $R^{d'}$ together represent a trimethylene group and $R^{e'}$ represents a protecting group,
with a compound of the general formula



IV

wherein R^{30} represents the side-chain of a natural α-amino acid in which any functional group is protected and R^4 has the significance given earlier or R^{30} and R^4 together represent a group of the formula $-(CH_2)_n-$ in which n has the significance given earlier and R^{50} has the same significance as R^5 earlier except that any carboxyl group is protected,
to give a compound of the general formula



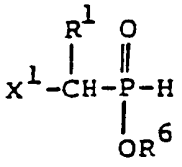
IIA

wherein R^1, R^2, R^4, R^5, R^{30}, R^{50} and X^1 have the significance given earlier,
and, where required, converting any protected carboxyl group R^{50} into a carboxyl group, if desired cleaving off the protecting group $R^{e'}$ and appropriately acylating or sulphonylating the resulting compound, if desired cleaving off any protecting group present on $R^{a'}$ and/or $R^{c'}$ and/or R^{30} and, also if desired, appropriately acylating or sulphonylating any amino group obtained or amidating any carboxyl group obtained.

The condensation of a compound of formula III with a compound of formula IV can be carried out in a manner which is known per se in peptide chemistry. Thus, for example, the condenstion can be carried out according to the acid halide, acid anhydride, activated amide, mixed carbonic anhydride or activated ester method. In a preferred procedure the condensation is carried out according to the activated ester method, particularly using hydroxybenzotriazole in the presence of a condensation agent such as N,N'-dicyclohexyl-carbodiimide.

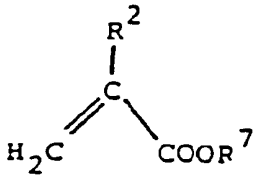
The subsequent steps which can be carried out on a condensation product of formula IIA are known per se in peptide chemistry and, accordingly, the methods used and the sequence in which the steps can be carried out will be familiar to any person skilled in the art.

The compounds of formula III hereinbefore can be prepared by reacting a compound of the general formula



V

wherein R^1, R^6 and X^1 have the significance given earlier,
with a compound of the general formula



VI

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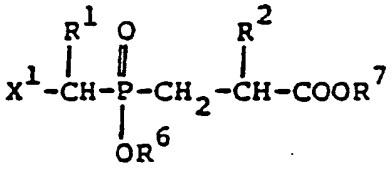
wherein R^2 has the significance given earlier and R^7 represents a protecting group (e.g. benzyl) which is selectively cleavable in the presence of R^6,
and cleaving off the prectecting group R^7 from the resulting compound of the general formula

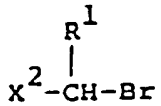


VII

wherein R^1, R^2, R^6, R^7 and X^1 have the significance given earlier.

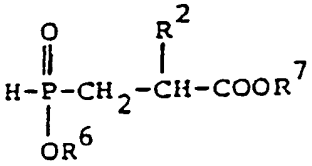
The reaction of a compound of formula V with a compound of formula VI and the cleavage of the protecting group R^7 from the resulting compound of formula VII can be carried out according to generally known methods.

The compounds of formula III in which X^1 represents a cyclic imido group as hereinbefore defined can also be prepared by reacting a compound of the general formula



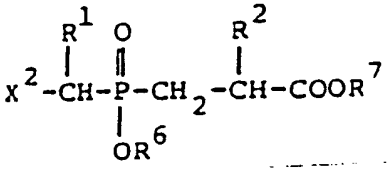
VIII

wherein R^1 has the significance given earlier and X^2 represents a cyclic imido group as hereinbefore defined,
with a compound of the general formula



IX

wherein R^2, R^6 and R^7 have the significance given earlier,
and cleaving off the protecting group R^7 from the resulting compound of the general formula

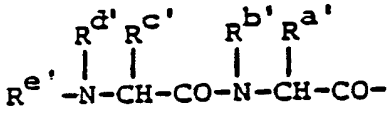


X

wherein R^1, R^2, R^6, R^7 and X^2 have the significance given earlier.

The reaction of a compound of formula VIII with a compound of formula IX and the cleavage of the protecting group R^7 from the resulting compound of formula X can be carried out according to generally known methods.

A further method for the preparation of the compounds of formula II hereinbefore comprises introducing a cyclic imido group or a group of the formula



(d)

wherein $R^{a'}$, $R^{b'}$, $R^{d'}$ and $R^{e'}$ have the significance given earlier,

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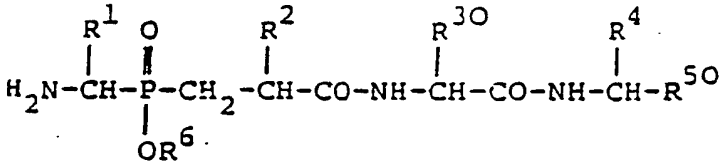
into a compound of the general formula



(XI)

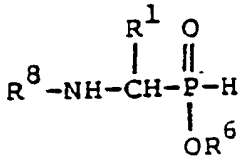
wherein R^1, R^2, R^4, R^6, R^{3o} and R^{5o} have the significance given earlier,
and, where required, converting any protected carboxyl group denoted by R^{5o} into a carboxyl group, if desired, cleaving off the protecting group $R^{6'}$ and appropriately acylating or sulphonylating the resulting compound, if desired cleaving off any protecting group present on $R^{a'}$ and/or $R^{c'}$ and/or R^{3o} and, also if desired, appropriately acylating or sulphonylating any amino group obtained or amidating any carboxyl group obtained.

The introduction of a cyclic imido group or a group of formula (d) into a compound of formula XI can be carried out in a manner known per se in peptide chemistry. For example, a cyclic imido group can be introduced by reacting a compound of formula XI with an anhydride derived from a aliphatic or aromatic dicarboxylic acid, an N-carboxyamino acid, an azadicarboxylic acid or an O-carboxyhydroxy acid in accordance with known methods. A group of formula (d) can be introduced by condensing a compound of formula XI with an appropriate dipeptide or, preferably, in two stages, by condensing a compound of formula XI with an appropriately protected natural α-amino acid, suitably deprotecting the condensation product and then condensing the deprotected compound obtained with a further appropriately protected natural α-amino acid. It will, of course, be appreciated that in this preferred procedure the protected natural α-amino acids used can be the same or different.

The subsequent steps which can be carried out on the product obtained after introduction of a cyclic imido group or a group of formula (d) are well known in peptide chemistry and, accordingly, the methods used and the sequence in which the steps can be carried out will be familiar to any person skilled in the art.

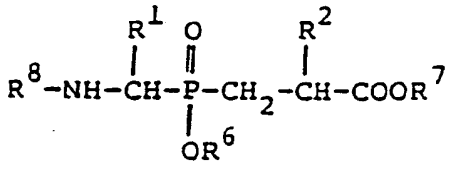
The compounds of formula XI can be prepared by treating a compound of formula IIA in which X^1 represents a phthalimido group with hydrazine in a known manner, for example using hydrazine hydrate in an inert organic solvent such as an alkanol (e.g. methanol, ethanol etc) at about room temperature.

The compounds of formula XI can also be prepared by reacting a compound of the general formula



XII

wherein R^1 and R^6 have the significance given earlier and R^8 represents a protecting group,
with a compound of formula VI hereinbefore, cleaving off the protecting group R^7 from the resulting compound of the general formula



XIII

wherein R^1, R^2, R^6 and R^8 have the significance given earlier,
condensing the resulting compound of the general formula

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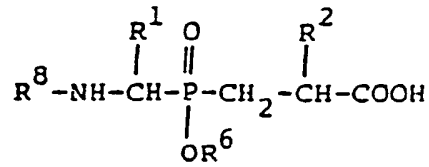
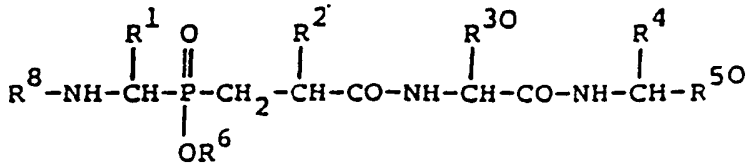


XIV

wherein R^1, R^2, R^6 and R^8 have the significance given earlier,
with a compound of formula IV hereinbefore and cleaving off the protecting group R^8 and converting any protected carboxyl group R^{50} into a carboxyl group in the thus-obtained compound of the general formula

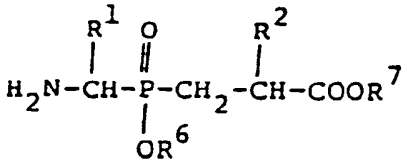


XV

wherein R^1, R^2, R^4, R^5, R^8, R^{30} and R^{50} have the significance given earlier.

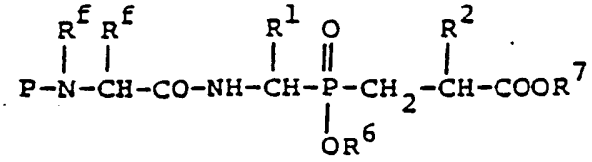
This latter procedure for the preparation of the compounds of formula XI can also be carried out according to generally known methods.

A further method for the preparation of compounds of formula III in which X^1 represents a group of formula (b) wherein P and Q together represent a group of the formula $-N(R^f)-CH(R^f)-$ comprises treating a compound of formula VII in which X^1 represents phthalimido with hydrazine, condensing the resulting compound of the general formula



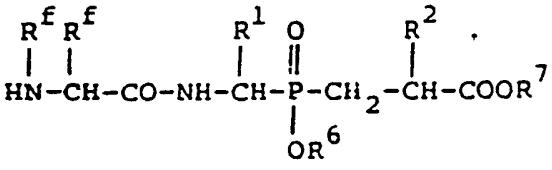
XVI

wherein R^1, R^2, R^6 and R^7 have the significance given earlier,
with an appropriately protected amino acid, treating the condensation product of the general formula



XVII

wherein R^1, R^2, R^5, R^7, and R^f have the significance given earlier and P represents a protecting group, removing the protecting group P, reacting the resulting compound of the general formula



XVIII

wherein R^1, R^2, R^6, R^7 and R^f have the significance given earlier,
with phosgene and cleaving off the protecting group R^7 from the resulting compound of the general formula

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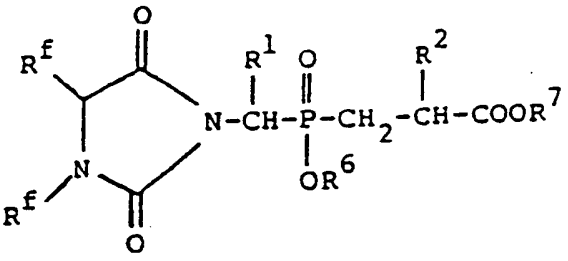

XIX

wherein R^1, R^2, R^6, R^7 and R^f have the significance given earlier.

This procedure for the preparation of a compound of formula III in which X^1 represents a group of formula (b) wherein P and Q together represent a group of the formula $-N(R^f-CH(R^f)-$ can be carried out according to known methods.

The compounds of formulae IV, V, VI, VIII, IX and XII hereinbefore are known compounds or analogues of known compounds which can be prepared in a similar manner to the known compounds or as described in the Examples hereinafter.

The compounds of formula I hereinbefore and their pharmaceutically acceptable salts inhibit the enzyme collagenase and can be used in the control or prevention of degenerative joint diseases such as rheumatoid arthritis and osteoarthritis.

The in vitro inhibitory activity of the present compounds can be demonstrated against collagenase obtained from a culture of human synovial fibroblasts according to the method of Dayer et al., Proc. Natl.Acad.Sci. USA (1976), 73, 945, following activation of the protrypsin. Collagenase activity was measured using ^{14}C-acetylated collagen type I from rat tail tendons as the substrate and employing the microtitre plate assay method of Johnson-Wint, B. Anal. Biochem. (1980), 104, 175. The IC_{50} is that concentration of a compound of the present invention in the enzyme digestion which reduces substrate cleavage and solubilization to 50% of that achieved by the enzyme alone.

The results obtained in the foregoing test with representative compounds of this invention are compiled in the Table I hereinafter:.

Table I

Compound of formula I	IC_{50}
A	5.6×10^{-8}
B	6×10^{-7}
C	1.6×10^{-7}
D	1.1×10^{-7}
E	2.2×10^{-7}

Compound A: N-[N-[(R or S)-2-[[[[[N-[1-(Benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl]-hydroxyphosphinyl]methyl]-4-methylvaleryl]-L-leucyl]-L-alanine.

Compound B: [(3-Aminophthalimido)methyl][(RS))-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid.

Compound C: [(RS)-4-Methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid.

Compound D: [(R or S)-4-Methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid.

Compound E: [[1,4-Dihydro-2,4-dioxo-3(2H)-quinazolinyl]methyl][[(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid.

The in vivo activity of the present compounds can be demonstrated using the following test procedure.

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Groups of female rats received an intradermal injection into the shaved backs of 10 x 0.1 ml of an emulsion of type II collagen/Freund's incomplete adjuvant. Ten days later the test compound was administered twice daily at a dosage of 20 mg kg^{-1} via indwelling jugular vein catheters; dosing was continued for 12 days. Groups of rats which received the intradermal injection, but which were not treated with test compounds, served as the control. The incidence of hind paw inflammation was assessed visually at intervals throughout the test and was expressed as the proportion of the group showing signs of erythema and/or swelling. Radiological change in the ankle region of the hind paws was assessed at the termination of the test and was quantified using an arbitrary scale from 0 = normal to 6 = severe change, results being expressed as group means. Statistical analysis was performed using the Mann-Whitney "U" test.

Table II

	Inflammation	Radiological scores	
	day 4	Talus	Tarsus
Control	8/11	2.28 ± 0.53	1.75 ± 0.45
Compound D	3/12	0.86 ± 0.34	0.64 ± 0.37

Compound D given in this Table is compound D named in connection with Table I earlier.

The compounds of formula I and their pharmaceutically acceptable salts can be used as medicaments in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. This carrier material can be organic or inorganic carrier material which is suitable for enteral or parenteral administration such as water, lactose, starch, magnesium stearate, talc, gum arabic, gelatine, polyalkylene glycols, petroluem jelly etc. The pharmaceutical preparations can be made up in a solid form (e.g. as tablets, powders, dragees, suppositories, capsules etc) or in a liquid form (e.g. as solutions, emulsions, suspensions etc).

If necessary, the pharmaceutical preparations can be subjected to conventional pharmaceutical operations such as sterilization and the like and they can also contain conventional pharmaceutical adjuvants such as preserving agents, stabilizing agents, wetting agents, salts for varying the osmotic pressure etc. The present pharmaceutical preparations may also contain other therapeutically active substances.

The pharmaceutical preparations can be manufactured by mixing a compound of formula I or a pharmaceutically acceptable salt thereof and, if desired, one or more other therapeutically active substances with a therapeutically inert carrier material and bringing the mixture obtained into a galenical administration form.

The compounds of formula I and their pharmaceutically acceptable salts may be administered to adults in a dosage range of from about 5 mg to 30 mg, preferably about 10 mg to 15 mg, per day. It will, of course be appreciated that this dosage range is given by way of example only and that it can be varied upwards or downwards depending on factors such as the potency of the particular compound or salt to be administered, the particular condition to be treated and the individual requirements of the patient as determined by the attending physician.

The following Examples illustrate the present invention. In these Examples, the structures of the compounds obtained were confirmed by nuclear magnetic resonance data, mass spectra and/or microanalyses.

Example I

(A) The preparation of the starting material:

(i) A mixture of 7.98 g (0.12 mol) of crystalline phos phinic acid and 15.96 g (0.15 mol) of trimethyl orthoformate was stirred at room temperature under nitrogen for 1 hour. The resulting solution was then added dropwise to a stirred mixture of 7.98 g (0.037 mol) of benzyl isobutylacrylate and 3.14 g (0.027 mol)

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of 1,1,3,3-tetramethylguanidine at such as rate that the temperature was maintained at 0-8°C by means of an external cooling bath. After completion of the addition the cooling bath was removed, the mixture was allowed to come to room temperature and was then stirred for 2 hours. The mixture was diluted with 250 ml of dichloromethane and the solution was washed with 200 ml of water and 200 ml of 10% sulphuric acid. The combined aqueous extracts were extracted with two 50 ml portions of dichloromethane and the combined dichloromethane extracts were washed with sodium chloride solution, dried over anhydrous sodium sulphate and evaporated to yield 12.62 g of a colourless oil containing benzyl 2-[-(methoxyphosphinyl)methyl]-4-methylvalerate.

(ii) 6.0 g of crude benzyl 2-[(methoxyphosphinyl)methyl]-4-methylvalerate were dissolved in 30 ml of dichloromethane and the solution was cooled in an ice-bath while stirring under nitrogen. 9 ml of bis-(trimethylsilyl)acetamide and 2.6 g of diisopropylethylamine were added, the mixture was stirred for 5 minutes and then 4.8 g of N-bromomethylphthalimide were added. The cooling bath was removed, the mixture was left to come to room temperature, stirred for 5 hours and then a further 20 ml of dichloromethane were added. The solution was washed with 50 ml of 10% sulphuric acid and 50 ml of sodium chloride solution, dried over anhydrous sodium sulphate and evaporated to give 8.6 g of a yellow oil which was purified by flash chromatography on silica gel using ethyl acetate/n-hexane (2:1) for the elution. There were obtained 4.22 g of benzyl 2(RS)-[[(RS)-(methoxy)(phthal imidomethyl)phosphinyl]methyl]-4-methylvalerate in the form of a colourless oil.

(iii) 4.5 g of benzyl 2(RS)-[[(RS)-(methoxy)(phthalimidomethyl)phosphinyl]methyl]-4-methylvalerate were dissolved in 200 ml of methanol and the solution was hydrogenated over 1.9 g of 10% palladium-on-charcoal for 3.5 hours. After filtration and evaporation of the filtrate there were obtained 3.0 g of a white foam containing 2(RS)-[[(RS)-(methoxy)(phthalimidomethyl)phosphinyl]methyl]-4-methylvaleric acid.

(iv) 3.0 g of 2(RS)-[[(RS)-(methoxy) (phthalimidomethyl)phosphinyl]methyl]-4-methylvaleric acid were dissolved in 50 ml of tetrahydrofuran and 1.65 g of L-leucine N-methylamide and 2.2 g of hydroxybenzotriazole were added while stirring. After all of the solids had dissolved 2.02 g of N,N'-dicyclohexylcarbondiimide were added and the mixture was stirred at room temperature overnight. The tetrahydrofuran was removed by evaporation, the residue was triturated with 100 ml of ethyl acetate and the mixture was filtered in order to remove dicyclohexylurea. The filtrate was washed twice with 50 ml of saturated sodium hydrogen carbonate solution each time, dried over anhydrous sodium sulphate and evaporated to give a yellow gum. This gum was purified by flash chromatography on silica gel using 5% methanol in ethyl acetate for the elution. There were obtained 3.32 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]-4-methylpentyl](phthalimidomethyl)phosphinic acid methyl ester in the form of a white foam.

(B) The process:

123 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-4-methylpentyl]-(phthalimidomethyl)phosphinic acid methyl ester were dissoved in a mixture of 3 ml of acetic acid and 3 ml of 48% hydrogen bromide in acetic acid and the mixture was left to stand at room temperature for 18 hours. The solvent was removed by evaporation, the residue was dissolved in a mixture of 10 ml of toluene and 5 ml of acetone and the solution was evaporated. This procedure was repeated twice and the residue was then dissolved in a mixture of 5 ml of dichloromethane and 3 ml of acetone and the solution was evaporated. After drying under a high vacuum (0.1 mmHg) there were obtained 115 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl](phthalimidomethyl)phosphinic acid in the form of an off-white foam.

Example 2

(A) The preparation of the starting material:

(i) 2.5 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-4-methylpentyl-(phthalimidomethyl)phosphinic acid methyl ester, prepared as described in Example 1(A) (v), were dissolved in 30 ml of a 0.33M solution of hydrazine hydrate in methanol. The mixture was stirred at room temperature for 18 hours and was then evaporated. The residue was suspended in 50 ml of dichloromethane and 0.7 g of glacial acetic acid was added. After standing at room temperature for 1 hour the precipitated phthalhydrazide was removed by filtration and the filtrate was evaporated to give a colourless

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gum which was purified by chromatography on silica gel using chloroform/methanol/acetic acid/water (60:18:2:3) for the elution. There were obtained 1.84 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester acetate in the form of a colourless gum.

(ii) 0.4 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbomoyl)butyl]carbamoyl]pentyl]-phosphinic acid methyl ester acetate was dissolved in 15 ml of dichloromethane and 0.12 g of maleic anhydride and 0.12 g of triethylamine were added. The mixture was stirred at room temperature for 1 hour and then diluted with 20 ml of dichloromethane. The solution was washed with 5 ml of 10% sulphuric acid, dried over anhydrous sodium sulphate and evaporated to give 0.31 g of a colourless gum which was dissolved in 5 ml of dimethylformamide. 0.135 g of hydroxybenzotriazole and 0.15 g of N,N'-dicyclohexylcarbodiimide were added to the dimethylformamide solution and the mixture was stirred at room temperature overnight. The dimethylformamide was removed by evaporation, the residue was triturated with 30 ml of ethyl acetate and the mixture was filtered in order to remove dicyclohexylurea. The filtrate was washed twice with 30 ml of saturated sodium hydrogen carbonate solution each time, dried over anhydrous sodium sulphate and evaporated to give a colourless gum. This gum was purified by flash chromatography on silica gel using 10% methanol in dichloromethane for the elution. There was obtained 0.155 g of (maleimido)[-(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester in the form of a colourless gum.

(B) The process:

60 mg of (maleimido)((RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid methyl ester were dissolved in 5 ml of dichloromethane and 0.5 ml of bromotrimethylsilane were added. After stirring at room temperature for 1.5 hours the solvent was removed by evaporation and the residue was re-evaporated twice with 20 ml of acetone each time. The residue was then dissolved in 5 ml of acetone and 0.25 ml of water. After standing at room temperature for 15 minutes the solvent was removed by evaporation, the residue was dissolved in 10 ml of dichloromethane and 50 mg of triethylamine were added. After 2 hours the solution was washed with 10 ml of sodium chloride solution and evaporated to give 75 mg of (maleimidomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid triethylamine salt in the form of a white foam.

Example 3

(A) The preparation of the starting material:

0.36 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid methyl ester acetate, prepared as described in Example 2(A) (i), was dissolved in 10 ml of dichloromethane and 0.17 g of succinic anhydride and 0.17 g of triethylamine were added. After stirring at room temperature for 2 hours 0.2 g of hydroxybenzotriazole and 0.2 g of N,N'-dicyclohexylcarbodiimide were added. The mixture was stirred at room temperature for 18 hours and then filtered in order to remove dicyclohexylurea. The filtrate was washed twice with 15 ml of saturated sodium hydrogen carbonate solution each time. After drying over anhydrous sodium sulphate the solvent was removed by evaporation to give a colourless gum. This gum was purified by flash chromatography on silica gel using ethyl acetate/methanol (8:1) for the elution. There was obtained 0.23 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl](succinimidomethyl)phosphinic acid methyl ester in the form of a white foam.

(B) The process:

60 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-(succinimidomethyl)phosphinic acid methyl ester were dissolved in 5 ml of dichloromethane, 0.5 ml of bromotrimethylsilane was added and the mixture was stirred at room temperature for 1.5 hours. The solvent was removed by evaporation and the residue was then re-evaporated twice with 20 ml of acetone each time. The residue was dissolved in 5 ml of acetone and 0.25 ml of water. After standing at room

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temperature for 15 minutes the solvent was removed by evaporation and the residue was dissolved in 20 ml of acetone/dichloromethane (1:2). The solution was then evaporated to give 56 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl](succinimidomethyl)phosphinic acid in the form of a white foam.

Example 4

(A) The preparation of the starting material:

In a manner analogous to that described in Example 3(A), from 0.7 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester acetate and 0.29 g of phenylmaleic anhydride there was obtained 0.21 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][2-phenylmaleimido)methyl]phosphinic acid methyl ester in the form of a pale yellow foam.

(B) The process:

0.1 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(2-phenylmaleimido)methyl]phosphinic acid methyl ester was dissolved in 1 ml of dichloromethane and 2 ml of trifluoroacetic acid were added. The mixture was stirred at room temperature for 2 hours and the solvent was then removed by evaporation. The residue was taken up in 30 ml of acetone/dichloromethane (1:1) and the solution was evaporated to give 95 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl][(2-phenylmaleimido)methyl]phosphinic acid in the form of a tan coloured foam.

Example 5

(A) The preparation of the starting material:

In a manner analogous to that described in Example 3 (A), from 0.4 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester acetate and 0.178 g of 3-methoxyphthalic anhydride there was obtained 0.1 g of [(3-methoxyphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester in the form of a colourless foam.

(B) The process:

0.1 g of [(3-methoxyphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid methyl ester was treated according to the procedure described in of Example 3(B) to give 95 mg of [(3-methoxyphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam.

Example 6

(A) The preparation of the starting material:

In a manner analogous to that described in Example 3(A), from 0.45 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester acetate and 0.185 g of 4-methoxyphthalic anhydride there was obtained 0.274 g of [(4-methoxyphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester in the form of colourless foam.

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(B) The process:

0.1 g of [(4-methoxyphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid methyl ester was treated according to the procedure described in Example 3(B) to give 94 mg of [(4-methoxyphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a colourless foam.

Example 7

(A) The preparation of the starting material:

In a manner analogous to that described in Example 3(A), from 0.285 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester acetate and 0.15 g of 1,8-naphthalic anhydride there was obtained 0.195 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl](1,8-naphthalendicarboximidomethyl)phosphinic acid methyl ester in the form of a pale yellow foam.

(B) The process:

0.16 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl](1,8-naphthalendicarboximidomethyl)phosphinic acid methyl ester was treated according to the procedure described in Example 3(B) to give 155 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl](1,8-naphthalendicarboximidomethyl)phosphinic acid in the form of a pale yellow foam.

Example 8

(A) The preparation of the starting material:

In a manner analogous to that described in Example 3(A), from 0.41 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester acetate and 0.21 g of 3-methyl-6-methoxyphthalic anhydride there was obtained 0.245 g of [(3-methoxy-6-methylphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester in the form of a white foam.

(B) The process:

0.1 g of [(3-methoxy-6-methylphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid methyl ester was treated according to the procedure described in Example 3(B) to give 95 mg of [(3-methoxy-6-methylphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam.

Example 9

(A) The preparation of the starting material:

(i) A solution of 0.53 g of N-[(benzyloxy)carbonyl]-L-leucine in 10 ml of dry tetrahydrofuran was cooled to -30°C and there was then added 0.23 g of N-ethylmorpholine followed by 0.27 g of isobutyl chloroformate. After stirring at -30°C for 5 minutes a solution of 0.6 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methlcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester, prepared as described in Example 2(A)(i), and 0.23 g of N-ethylmorpholine were added. The mixture was left to come to room temperature and was stirred at this temperature for 3.5 hours. The mixture was then diluted with 50 ml of dichloromethane, washed with 20 ml of 10% sulphuric acid, 20 ml of sodium chloride solution and 20 ml of saturated sodium hydrogen carbonate solution, dried over anhydrous sodium sulphate and evaporated to

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give a colourless gum. This gum was purified by flash chromatography on silica gel using 10% methanol in ethyl acetate for the elution to give 0.645 g of benzyl[(S)-1-[[[methoxy[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinyl]methyl]carbamoyl]-3-methylbutyl]carbamate in the form of a white foam.

(ii) 0.75 g of benzyl[(S)-1-[[[methoxy[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinyl]methyl]carbamoyl]-3-methylbutyl]carbamate hydrochloric acid. The solution was hydrogenated over 0.1 g of 10% palladium-on-charcoal for 4 hours. After filtration and evaporation the residue was re-evaporated three times with 30 ml of toluene each time in order to remove water. The white residue obtained was dissolved in 10 ml of dimethylformamide and the solution was cooled to 0°C. 0.375 g of N-benzyloxycarbonyl-L-proline, 180 mg of N-ethylmorpholine and 0.4 g of hydroxybenzotriazole were added and, after all of the solids had dissolved, 0.345 g of N,N'-dicyclohexylcarbodiimide was added. After stirring at room temperature for 18 hours the solvent was removed by evaporation, the residue was triturated with 30 ml of ethyl acetate and the mixture was filtered in order to remove dicyclohexylurea. The filtrate was washed twice with 30 ml of saturated sodium hydrogen carbonate solution each time, dried over anhydrous sodium sulphate and evaporated to give a colourless gum which was purified by flash chromatography on silica gel using 15% methanol in ethyl acetate for the elution. There was obtained 0.98 g of benzyl(S)-2-[[(S)-1-[[[methoxy[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinyl]methyl]carbamoyl]-3-methylbutyl]carbamoyl]-1-pyrrolidinecarboxylate in the form of a white foam.

(iii) 0.53 g of benzyl[(S)-2-[[(S))-1-[[[methoxy[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinyl]methyl]carbamoyl]-3-methylbutyl]carbamoyl]-1-pyrrolidinecarboxylate was dissolved in 50 ml of methanol containing 0.8 ml of 1M hydrochloric acid. The solution was hydrogenated over 0.1 g of 10% palladium-on-charcoal for 4 hours. After filtration and evaporation of the filtrate the residue was re-evaporated three times with 30 ml of toluene each time in order to remove water. The white residue obtained was dissolved in a mixture of 3 ml of dimethylformamide and 10 ml of dichloromethane. The solution was treated with 0.15 g of acetic anhydride and 0.2 g of triethylamine and the mixture was stirred for 2 hours. The solvent was then removed by evaporation, the residue was taken up in 30 ml of ethyl acetate and the mixture was filtered in order to remove triethylamine hydrochloride. The filtrate was then evaporated and the residue was purified by flash chromatography using ethyl acetate/methanol (5:2) for the elution to give 0.43 g of [[(N)-(1-acetyl-L-prolyl)-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester in the form of a white foam.

(B) The process:

0.1 g of [[[N-(1-acetyl-L-prolyl)-L-leucyl]amino]methyl[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester was treated according to the procedure described in Example 3(B) to give 95 mg of [[[N-(1-acetyl-L-prolyl)-L-leucyl]amino]methyl[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of an off-white foam.

Example 10

0.11 g of benzyl(S)-2-[[(S)-1-[[[methoxy(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinyl]methyl]carbamoyl]-3-methylbutyl]carbamoyl]-1-pyrrolidinecarboxylate was dissolved in 4 ml of dichloromethane and 0.5 ml of bromotrimethylsilane was added. The mixture was stirred at room temperature for 1.5 hours and the solvent was removed by evaporation. The residue was dissolved in 5 ml of acetone and there were then added 1 ml of water and 0.5 g of sodium hydrogen carbonate followed by 50 mg of benzyl chloroformate. After stirring at room temperature for 2.5 hours the solvent was removed by evaporation, the residue was dissolved in 15 ml of 1M sodium hydroxide solution and the resulting solution was extracted three times with 15 ml of diethyl ether each time. The aqueous solution was acidified with 10% sul phuric acid, saturated with sodium chloride solution and extracted five times with 20 ml of 5% methanol in dichloromethane each time. The organic extracts were dried over anhydrous sodium sulphate and evaporated to give 0.1 g of [[[N-(1-[(benzyloxy)carbonyl]-L-prolyl-L-leucyl]amino]methyl[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam.

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Example 11

(A) The preparation of the starting material:

(i) 1.06 g of L-leucyl-L-alanine ethyl ester hydrochloride and 1.46 g of 2(RS)-[[(RS) -(methoxy)-(phthalimidomethyl)phosphinyl]methyl]-4-methylvaleric acid, prepared as described in Example 1(A)(iii), were dissolved in 12 ml of dimethylformamide. The solution was cooled to 0°C. 1.08 g of hydroxybenzotriazole and 0.46 g of N-ethylmorpholine were added and, after all of the solids had dissolved, 0.88 g of N,N'-dicyclohexylcarbodiimide was added. The mixture was stirred at room temperature for 18 hours, the solvent was then removed by evaporation, the residue was triturated with 50 ml of ethyl acetate and the mixture was filtered in order to remove dicyclohexylurea. The filtrate was washed twice with 50 ml of saturated sodium hydrogen carbonate solution each time, dried over anhydrous sodium sulphate and evaporated to give a yellow gum. This gum was purified by flash chromatography using ethyl acetate for the elution. There was obtained 1.06 g of [(R or S)-2-[[(S)-1-[[(S)-1-(ethoxycarbonyl)ethyl]carbamoyl]-3-methylbutyl]carbamoyl]-4-methylpentyl](phthalimidomethyl)phosphinic acid methyl ester hydrochloride in the form of a white foam.

(ii) The mixture of the four isomers prepared in paragraph (i) was separated by repeated flash chromatography on silica gel using ethyl acetate for the elution followed by fractional crystallization of enriched fractions from diethyl ether/n-hexane. The four isomers were designated as isomers A, B, C and D in the order of elution from the column.

Isomer A: m.p. 149-150°C;
Isomer B: m.p. 164-165°C;
Isomer C: m.p. 174-176°C;
Isomer D: m.p. 93-95°C.

(B) The process:

(a) A mixture of 0.1 g of isomers A and B, prepared as described in paragraph (ii) was treated according to the procedure described in Example 3(B) to give 95 mg of [(R or S)-2-[[(S)-1-[[(S)-1-(ethoxycarbonyl)ethyl]carbamoyl]-3-methylbutyl]carbamoyl]-4-methylpentyl](phthalimidomethyl)phosphinic acid in the form of a white foam.

(b) A mixture of 0.1 g of isomers C and D, prepared as described in paragraph (ii), was treated according to the procedure described in Example 3(B) to give 95 mg of [(R or S)-2-[[(S)-1-[[(S)-1-(ethoxycarbonyl)ethyl]carbamoyl]-3-methylbutyl]carbamoyl]-4-methylpentyl](phthalimidomethyl)phosphinic acid in the form of a white foam.

Example 12

(A) The preparation of the starting material:

(i) A mixture of 0.65 g of isomers C and D, prepared as described in Example 11(A)(ii), was treated in a manner analogous to that described in Example 2(A)(i) to give 0.47 g of N-[N-[(R or S)-2-[[(aminomethyl)-methoxyphosphinyl]methyl]-4-methylvaleryl]-L-leucyl]-L-alanine ethyl ester acetate in the form of a colourless gum.

(ii) 0.45 g of N-[N-[(R or S)-2-[[(aminomethyl)methoxyphosphinyl]methyl]-4-methylvaleryl]-L-leucyl]-L-alanine ethyl ester acetate was treated in a manner analogous to that described in Example 9(A)(i) to give 0.6 g of N-[N-[(R or S)-2-[[[[[N-[(benzyloxy)carbonyl]-L-leucyl]amino]methyl]methoxyphosphinyl]methyl]-4-methylvaleryl]-L-leucyl]-L-alanine ethyl ester in the form of a white foam.

(iii) 0.6 g of N-[N-[(R or S)-2-[[[[[N-[(benzyloxy)carbonyl]-L-leucyl]amino]methyl]methoxyphosphinyl]-methyl]-4-methylvaleryl]-L-leucyl]-L-alanine ethyl ester was treated in a manner analogous to that described in Example 9(A)(ii) to give 0.52 g of N-[N-[(R or S)-2-[[[[[N-[1-(benzyloxy)carbonyl]-L-prolyl]-L-leucyl]-amino]methyl]methoxyphosphinyl]methyl]-4-methylvaleryl]-L-leucyl]-L-alanine ethyl ester in the form of a white foam.

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(B) The process:

0.11 g of N-[N-[(R or S)-2-[[[[[N-[1-[(benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl]-methoxyphosphinyl]methyl]-4-methylvaleryl]-L-leucyl]-L-alanine was treated in a manner analogous to that described in Example 10 to give 70 mg of N-[N-[(R or S)-2-[[[[[(N-[1-[(benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl]methoxyphosphinyl]methyl]-4-methylvaleryl]-L-leucyl]-L-alanine in the form of a white foam.

Example 13

(A) The preparation of the starting material:

(i) 0.6 g of [(-)-1-[1-(benzyloxy)formamido]ethyl]phosphinic acid was dissolved in 7 ml of dry tetrahydrofuran containing 0.126 g of ethanol and 0.54 g of N,N'-dicyclohexylcarbodiimide and 0.03 g of dimethylaminopyridine were added. The mixture was stirred at room temperature for 4 hours, filtered and the filtrate was evaporated. The residue was dissolved in 50 ml of ethyl acetate and the solution was washed with 20 ml of 5% potassium hydrogen sulphate solution, then with 20 ml of saturated sodium hydrogen carbonate solution and finally with 20 ml of sodium chloride solution. After drying over magnesium sulphate the solution was evaporated, the residue was dissolved in 20 ml of diethyl ether, the solution was filtered and the filtrate was evaporated to give 0.4 g of an oil; Rf = 0.55 (2% methanol in ethyl acetate). This oil was mixed with 0.136 g of 1,1,3,3-tetramethylguanidine and 0.322 g of benzyl isobutylacrylate and the mixture was stirred at room temperature for 18 hours. The mixture was diluted with 25 ml of ethyl acetate and the solution was washed in succession with 10 ml of 10% hydrochloric acid, 10 ml of water and 10 ml of sodium chloride solution. After drying the solvent was removed by evaporation to give an oil which was purified by flash chromatography on silica gel using ethyl acetate for the elution. There was obtained 0.446 g of benzyl (RS)-2-[[[(R or S)-1-[1-(benzyloxy)formamido]ethyl]ethoxyphosphinyl]-methyl]-4-methylvalerate in th form of a colourless oil.

(ii) 0.446 g of benzyl (RS)-2-[[[(R or S)-1-[1-(benzyloxy)formamido)ethyl]ethoxyphospinyl]methyl]-4-methylvalerate was dissolved in 4 ml of ethanol containing 0.91 ml of 1M sodium hydroxide solution. The mixture was stirred at room temperature for 18 hours and then diluted with 25 ml of water. The solution was washed twice with 25 ml of diethyl ether each time and then acidified by the dropwise addition of concentrated hydrochloric acid. The aqueous solution was extracted three times with 15 ml of ethyl acetate each time and the combined organic extracts were washed with 15 ml of sodium chloride solution, dried over anhydrous sodium sulphate and evaporated to give 0.246 g of a colourless gum. This gum was dissolved in 5 ml of dichloromethane and 0.087 g of L-leucine N-methylamide was added. The solution was cooled to 0°C and 0.089 g of hydroxybenzotriazole was added. After all of the solid had dissolved 0.149 g of N,N'-dicyclohexylcarbodiimide was added and the mixture was stirred at room temperature for 18 hours. The solvent was removed by evaporation, the residue was triturated with 25 ml of ethyl acetate and the mixture was filtered in order to remove dicyclohexylurea. The solution was washed with 10 ml of saturated sodium hydrogen carbonate solution, dried over anhydrous sodium sulphate and evaporated to give a gum which was purified by flash chromatography on silica gel using 3% methanol in ethyl acetate for the elution. There was obtained 0.16 g of benzyl[(R or S)-1-[ethoxy-[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinyl]ethyl]carbamate in the form of a colourless gum.

(iii) 0.16 g of benzyl[(R or S)-1-[ethoxy-[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinyl]ethyl]carbamate was dissolved in 0.28 ml of ethanol containing 1M hydrochloric acid and 0.015 g of 5% palladium-on-charcoal and the mixture was hydrogenated for 2.5 hours. After filtration the filtrate was evaporated and the residue was re-evaporated twice with 25 ml of dichloromethane each time in order to remove water. The product was dissolved in 5 ml of dry tetra hydrofuran and 0.057g of triethylamine and 0.046 g of phthalic anhydride were added. The mixture was stirred at room temperature for 2 hours and then 0.076 g of hydroxybenzotriazole and 0.064 g of N,N'-dicyclohexylcarbodiimide were added. After stirring at room temperature for 18 hours the solvent was removed by evaporation, the residue was triturated with 20 ml of ethyl acetate and the mixture was filtered in order to remove dicyclohexylurea. The filtrate was washed twice with 10 ml of saturated sodium hydrogen carbonate solution each time, dried over anhydrous sodium sulphate and evaporated to give a gum which was purified by flash chromatography on silica gel using 1% methanol in ethyl acetate for the elution. There was obtained 0.078 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(R or S)-1-phthalimidoethyl]phosphonic acid ethyl ester in the form of a colourless foam.

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(B) The process:

78 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(R or S)-1-phthalimidoethyl]phosphinic acid ethyl ester were treated according to the procedure described in Example 1(B) to give 73 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(R or S)-1-phthalimidoethyl]phosphinic acid in the form of a white foam.

Example 14

(A) The preparation of the starting material:

In a manner analogous to that described in Example 13(A), from 0.6 g of [(+)-1-[1-(benzyloxy)-formamido]ethyl]phosphinic acid there was obtained 0.15 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(R or S)-1-phthalimidoethyl]phosphinic acid ethyl ester in the form of a white foam.

(B) The process:

0.1 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(R or S)-1-phthalimidoethyl]phosphinic acid ethyl ester was treated according to the procedure described in Example 1(B), to give 95 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(R or S)-1-phthalimidoethyl]phosphinic acid in the form of a white foam.

Example 15

(A) The preparation of the starting material:

(i) Racemic 3-amino-2-azacyclotridecanone was resolved into its optical isomers via the formation of the dibenzoyl tartrate salt followed by successive crystallizations from ethanol. From 13.2 g of the racemic amine and 23.4 g of (-)-dibenzoyltartaric acid there were obtained, after three crystallizations from ethanol, 6.04 g of tartrate salt with $[\alpha]_D^{20}$ = -115.3° (c = 1% in methanol).

An analogous procedure using (+)-dibenzoyltartaric acid gave tartrate salt with $[\alpha]_D^{20}$ = +115.0° (c = 1% in methanol).

20.0 g of the tartrate salt with $[\alpha]_D^{20}$ = -115.3° were suspened in 400 ml of chloroform and the suspension was shaken with 400 ml of saturated sodium hydrogen carbonate solution until a clear solution was obtained. After separation of the organic layer the aqueous solution was extracted with 100 ml of chloroform. The combined organic phases were dried over magnesium sulphate and evaporated to give 7.85 g of (-)-3-amino-2-azacyclotridecanone of melting point 128-130°C; $[\alpha]_D^{20}$ = -63.6° (c = 1% in methanol).

(ii) In an analogous manner to that described in Example 1(A)(iv), from 0.367 g of 2(RS)-[[(RS)-(methoxy)(phthalimidomethyl)phosphinyl]methyl]-4 -methylvaleric acid and 0.2 g of (-)-3-amino-2-azacyclotridecanone there was obtained 0.21 g of [(RS)-4-methyl-2-[[(R or S)-2-oxoazacyclotridecyl]-carbamoyl]pentyl](phthalimidomethyl)phosphinic acid methyl ester in the form of a white solid.

(B) The process:

75 mg of [(RS)-4-methyl-2-[[(R or S)-2-oxoazacyclotridecyl]carbamoyl]pentyl](phthalimidomethyl)-phosphinic acid methyl ester were treated according to the procedure described in Example 3(B), paragraph (ii) to give 72 mg of [(RS)-4-methyl-2-[[(R or S)-2-oxoazacyclotridecyl]carbamoyl]pentyl]-(phthalimidomethyl)phosphinic acid in the form of a white foam.

Example 16

BNSDOCID: <EP___0276436A1_I_>

(A) The preparation of the starting material:

In a manner analogous to that described in Example 3(A), from 0.64 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester acetate and 0.4 g of 3-(benzyloxy)phthalic anhydride there was obtained 0.347 g of [[3-(benzyloxy)phthalimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester in the form of a white foam.

(B) The process

0.1 g of [[3-(benxyloxy)phthalimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid methyl ester was treated according to the procedure described in Example 3(B) to give 95 mg of [[3-(benzyloxy)phthalimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam.

Example 17

0.2 g of [[3-(benzyloxy)phthalimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid was dissolved in 50 ml of methanol containing 0.1 g of 10% palladium-on-charcoal. The mixture was hydrogenated for 4 hours and then filtered. The filtrate was evaporated to give 0.16 g of [(3-hydroxyphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid in the form of an off-white foam.

Example 18

(A) The preparation of the starting material:

In a manner analogous to that described in Example 3(A), from 0.23 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester acetate and 0.105 g of 3-nitrophthalic anhydride there was obtained 0.105 g of [4-methyl-2-[[3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl][(3-nitrophthalimido)methyl]phosphinic acid methyl ester in the form of a pale yellow foam.

(B) The process:

0.1 g of [4-methyl-2-[[3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][3-nitrophthalimido)methyl]-phosphinic acid methyl ester was treated according to the procedure described in Example 3(B) to give 95 mg of [4-methyl-2-[[3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(3-nitrophthalimido)methyl]-phosphinic acid in the form of a pale yellow foam.

Example 19

75 mg of [4-methyl-2-[[3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(3-nitrophthalimido)-methyl]phosphinic acid were dissolved in 2.5 ml of methanol containing 0.01 g of 10% palladium-on-charcoal. The mixture was hydrogenated for 3 hours and then filtered. The filtrate was evaporated to give 70 mg of [(3-aminophthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl -1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid in the form of a yellow foam.

Example 20

BNSDOCID: <EP___0276436A1_I_>

(A) The preparation of the starting material:

(i) In a manner analogous to that described in Example 1(A)(i)-(iv), from 10.95 g of crystalline phosphinic acid acid, 10.99 g of benzyl isobutylacrylate and 30.31 g of triethyl orthoformate there were obtained 3.2 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-4-methylpentyl]-(phthalimidomethyl)phosphinic acid ethyl ester in the form of a white foam.

(ii) 3.2 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-4-methylpentyl](phthalimidomethyl)phosphinic acid ethyl ester were treated in a manner analogous to that described in Example 2(A)(i), with the exception that a 0.33M solution of hydrazine hydrate in ethanol was used, to give 2.06 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid ethyl ester acetate in the form of a white foam.

(iii) In a manner analogous to that described in Example 3(A), from 0.52 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester acetate and 0.34 g of diphenylmaleic anhydride there was obtained 0.581 g of [(2,3-diphenylmaleimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester in the form of a yellow-green foam.

(B) The process:

0.1 g of [(2,3-diphenylmaleimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl)pentyl]phosphinic acid ethyl ester was treated according to the procedure described in Example 4(B) to give 95 mg of [(2,3-diphenylmaleimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid in the form of a yellow-green foam.

Example 21

(A) The preparation of the starting material:

In a manner analgous to that described in Example 3(A), from 0.5 g of (aminomethyl)[(RS)-4-methyl-2-[-[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester acetate and 0.27 g of 3,6-dimethoxyphthalic anhydride there was obtained 0.325 g of [(3,6-dimethoxyphthalimido)methyl][(RS)-4-methyl -2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester in the form of a pale yellow foam.

(B) The process:

0.1 g of [(2,6-dimethoxyphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid ethyl ester was treated according to the procedure described in Example 3(B) to give 95 mg of [(3,6-dimethoxyphthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a yellow foam.

Example 22

(A) The preparation of the starting material:

In a manner analogous to that described in Example 3(A), from 0.528 g of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester acetate and 0.273 g of 2,3-naphthalic anhydride there was obtained 0.387 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl](2,3-naphthalenedicarboximidomethyl)phosphinic acid ethyl ester in the form of a white foam.

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(B) The process:

0.1 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl](2,3-naphthalenedicarboximidomethyl)phosphinic acid ethyl ester was treated according to the procedure described in Example 3(B) to give 95 mg of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl](2,3-naphthalenedicarboximidomethyl)phosphinic acid in the form of a white foam.

Example 23

(A) The preparation of the starting material:

(i) In a manner analogous to that described in Example 1(A)(iv), from 1.9 g of 2(RS)-[[(RS) -(ethoxy)-(phthalimidomethyl)phosphinyl]methyl]-4 -methylvaleric acid and 1.0 g of (-)-3-amino-2-azacyclotridecanone there were obtained 2.1 g of (RS)-[(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]-(phthalimidomethyl)phosphinic acid ethyl ester in the form of a white solid.

(ii) The mixture of the four isomers prepared as described in the preceeding paragraph was separated by repeated flash chromatography on silica gel using 30% acetone in dichloromethane for the elution. The four isomers were designated as isomers A, B, C and D in the order of elution from the column. From 3.5 g of the mixture there was obtained 1 g of a mixture of isomers B and C.

(iii) 0.5 g of a mixture of isomers B and C was treated in a manner analogous to that described in Example 20(A)(ii) to give (aminomethyl)[(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]-pentyl[phosphinic acid ethyl ester acetate in the form of a white gum which was then treated with 0.2 g of 1,8-naphthalic anhydride in a manner analogous to that described in Example 3(A) to give 0.355 g of [(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)-phosphinic acid ethyl ester in the form of a white solid.

(B) The process:

0.16 g of [(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid ethyl ester was dissolved in of 2 ml of acetic acid containing 48% hydrogen bromide and the solution was stirred at room temperature for 18 hours. After evaporation the solidresidue was triturated with 20 ml of diethyl ether, the solidwas filtered off and dried in vacuo at 60°C to give 0.145 g of [(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid in the form of a white powder of melting point 268-269°C.

Example 24

(A) The preparation of the starting material:

0.155 g (1 mmol) of isobutylmaleic anhydride and 0.42 g (1 mmol) of (aminomethyl)[(RS)-4-methyl-2-[[-(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester acetate were dissolved in 5 ml of dry tetrahydrofuran and the solution was stirred at room temperature for 2 hours in the presence of 0.202 g (2 mmol) of triethylamine. Subsequently, 0.27 g (2 mmol) of hydroxybenzotriazole and 0.206 g (1 mmol) of N,N'-dicyclohexylcarbodiimide were added. The mixture was stirred at room temperature for 18 hours. Dicyclohexylurea was removed by filtration and the filtrate was evaporated. The residue was taken up in 50 ml of ethyl acetate and the solution was washed in sequence with 5% citric acid solution and saturated sodium hydrogen carbonate solution and then dried over anhydrous sodium sulphate. After removal of the solvent by evaporation there was obtained 0.35 g of a solid which was chromatographed on silica gel using 1% methanol in chloroform for the elution. There were obtained 165 mg of [(2-isobutyl-maleimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester in the form of a foam.

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(B) The process:

0.145 g (0.239 mmol) of [(2-isobutylmaleimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid methyl ester was dissolved in 3 ml of trifluoroacetic acid and the solution was stirred at room temperature for 5 hours. After evaporation the crude product was chromatographed on silica gel using chloroform/methanol/acetic acid/water (120:15:3:2) for the elution. There were obtained 70 mg of [(2-isobutylmaleimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a foam.

Example 25

(A) The preparation of the starting material:

In a manner analogous to that described in Example 24(A), from 0.161 g (1.41 mmol) of glutaric anhydride and 0.41 g (0.94 mmol) of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester acetate there was obtained 0.124 g of (glutarimidomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester.

(B) The process:

0.11 g (0.23 mmol) of (glutarimidomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester was dissolved in 4 ml of dichloromethane and the solution was stirred overnight in the presence of 2 ml of bromotrimethylsilane. The solvent was removed by evaporation and the residue was dissolved in 5 ml of acetone/water (9:1). The solvent was removed by evaporation and this treatment was repeated once more to give 0.1 g of (glutarimidomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a foam.

Example 26

(A) The preparation of the starting material"

In a manner analogous to that described in Example 24(A), from 0.17 g (1.09 mmol) of 2(S)-isobutylsuccinic anhydride and 0.32 g (0.73 mmol) of (aminomethyl)[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester acetate there was obtained 0.16 g of [-[(S)-2-isobutylsuccinimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid ethyl ester.

(B) The process:

The product obtained according to the preceding paragraph in 2 ml of dichloromethane was treated overnight with 2 ml of bromotrimethylsilane. The solvent was removed by evaporation and the residue was treated with 5 ml of acetone/water (9:1). The solvent was removed by evaporation and the crude product was purified by chromatography on silica gel using chloroform/methanol/acetic acid/water (90:21:3:2) for the elution to give 0.09 g of [[(S)-2-isobutylsuccinimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid.

The 2(S)-isobutylsuccinnic anhydride used in part (A) of this Example was prepared as follows:

(i) 2.5 g (8.1 mmol) of 1-(4-nitrobenzyl) hydrogen 2(S)-isobutylsuccinnate were dissolved in 10 ml of tetrahydrofuran and the solution was stirred at room temperature for 3 hours in the presence of 4 ml of 4M sodium hydroxide solution. The solvent was removed by evaporation, the residue was dissolved in 20 ml of water and the solution was extracted three times with 25 ml of diethyl ether each time. The aqueous solution was acidified with 2M hydrochloric acid and the product was extracted with diethyl ether. The diethyl ether extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulphate. The solvent was removed by evaporation to yield 1.3 g of 2(S)-isobutylsuccinnic acid in

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the form of a gum.

(ii) 0.19 g (1.1 mmol) of 2(S)-isobutylsuccinnic acid was dissolved in 5 ml of dichloromethane and the solution was cooled to 0°C. 0.255 g (1.1 mmol) of N,N'-dicyclohexylcarbodiimide was added and the mixture was stirred at room temperature overnight. Dicyclohexylurea was removed by filtration and the filtrate was evaporated to give 0.17 g of 2(S)-isobutylsuccinnic anhydride in the form of a gum; IR 1800 cm^{-1}.

Example 27

In a manner analogous to that described in Example 26, there was prepared [[(R)-2-isobutylsuccinimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid.

Example 28

(A) The preparation of the starting material:

(i) 3 g (6.4 mmol) of benzyl 2(RS)-[[(RS)-(ethoxy)(phthalimidomethyl)phosphinyl]methyl]-4 -methylvalerate were dissolved in 39 ml (12.8 mmol) of a 0.33M solution of hydrazine hydrate in ethanol. The solution was stirred at room temperature overnight. The solvent was removed by evaporation and traces of hydrazine were removed by treatment with toluene followed by evaporation. The residue was taken up in 50 ml of dichloromethane and stirred at room temperature for 45 minutes in the presence of 5 ml of glacial acetic acid. The solid was removed by filtration and the filtrate was evaporated to give 2.56 g of benzyl 2(RS)-[[(RS) -(aminomethyl)(ethoxy)phosphinyl]methyl]-4-methylvalerate in the form of a gum.

(ii) 1.3 g (6.34 mmol) of phthalylglycine were dissolved in 10 ml of tetrahydrofuran, the solution was cooled in an ice-salt bath and then treated with 0.86 g (6.4 mmol) of hydroxybenzotriazole and 1.3 g (6.4 mmol) of N,N'-dicyclohexylcarbodiimide. The mixture was stirred at room temperature for 5 hours and dicyclohexylurea was then removed by filtration. The filtrate was evaporated, the resulting gum was dissolved in 10 ml of tetrahydrofuran and the solution was treated at 0°C with 2.5 g (6.2 mmol) of benzyl 2-(RS)-[[(RS) -(aminomethyl)(ethoxy)phosphinyl]methyl]-4-methylvalerate and 0.75 g (6.5 mmol) of N-ethyl-morpholine. The solution was stirred at room temperature overnight and the solvent was removed by filtration. The residue was taken up in 100 ml ethyl acetate, washed in sequence with 5% citric acid solution, 5% sodium hydrogen carbonate solution and water, dried over anhydrous sodium sulphate and evaporated to give a gum. Chromatography of this gum on silica gel using chloroform/methanol (98:2) for the elution gave 0.95 g of benzyl 2(RS)-[[(RS)--(ethoxy)[(2 -phthalimidoacetamido)methyl]phosphinyl]-methyl]-4 -methylvalerate.

(iii) 0.95 g (1.8 mmol) of benzyl 2(RS)-[[(RS)-(ethoxy)[(2-phthalimidoacetamido)methyl]phosphinyl]-methyl]-4-methylvalerate was treated with 11 ml (3.6 mmol) of a 0.33M solution of hydrazine hydrate in ethanol. After stirring at room temperature overnight the mixture was worked-up as described in paragraph (i) of this Example. Purification by chromatography on silica gel using chloroform/ methanol/acetic acid/water (120:15:3:2) for the elution gave 0.43 g of benzyl 2(RS)-[[[(RS) -(2-aminoacetamido)methyl]-(ethoxy)phosphinyl]methyl]-4 -methylvalerate acetate in the form of a gum.

(iv) 0.4 g (0.87 mmol) of benzyl 2(RS)-[[[(RS)-(2-aminoacetamido)methyl](ethoxy)phosphinyl]methyl]-4-methylvalerate acetate was dissolved in 170 ml of dry toluene and the solution was heated at 110°C in the presence of 0.125 g (1.24 mmol) of triethylamine and 4 ml (7.72 mmol) of a 1.93M solution of phosgene in toluene. After 15 minutes the solvent was removed by evaporation, the residue was dissolved in 10 ml of dry toluene and the solution was evaporated. The residue was then dissolved in 5 ml of dry dichloromethane and the solution was stirred at room temperature for 2 hours in the presence of 0.125 g (1.24 mmol) of triethylamine. 25 ml of dichloromethane were added and the solution was washed with water and sodium chloride solution, dried over anhydrous sodium sulphate and evaporated to give a gum. Chromatography of this gum on silica gel using chloroform/methanol (19:1) for the elution gave 0.3 g of benzyl 2(RS)-[-[(RS)-(ethoxy)[(2,5-dioxo-1 -imidazolidinyl)methyl]phosphinyl]methyl]-4-methylvalerate in the form of a gum.

(v) 0.27 g (0.64 mmol) of benzyl 2(RS)-[[(RS)-(ethoxy)[(2,5-dioxo-1 -imidazolidinyl)methyl]phosphinyl]-methyl]-4-methylvalerate was dissolved in 10 ml of ethanol and the solution was hydrogenated in the presence of 0.2 g of 10% palladium/carbon at room temperature and under atmospheric pressure. After 1 hour the catalyst was removed by filtration and the solvent was evaporated to give 0.22 g of 2(RS)-[[(RS)-

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(ethoxy)[2,5-dioxo-1-imidazolidinyl)methyl]phosphinyl]methyl]-4-methylvaleric acid in the form of a foam.

(vi) 0.22 g (0.64 mmol) of 2(RS)-[[(RS)-(ethoxy)[(2,5-dioxo-1 -imidazolidinyl)methyl]phosphinyl]methyl]-4-methylvaleric acid and 0.116 g (0.81 mmol) of L-leucine methylamide were taken up in 5 ml of dichloromethane and 2.5 ml of tetrahydrofuran. The solution was treated at -8°C with 0.3 g (1.2 mmol) of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroxyquinoline. The mixture was stirred at room temperature for 24 hours and was then left to stand at 9°C for 48 hours. The solvent was removed by evaporation, the residue was taken up in 50 ml of chloroform, the solution was washed in sequence with 5% citric acid solution, 5% sodium hydrogen carbonate solution and sodium chloride solution, dried over anhydrous sodium sulphate and evaporated to give a gum. This gum was chromatographed on silica gel using chloroform/methanol (19:1) for the elution to give 0.08 g of [(2,5-dioxo-1-imidazolidinyl)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester as a gum.

(B) The process:

60 mg (0.13 mmol) of [(2,5-dioxo-1-imidazolidinyl)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl[carbamoyl]pentyl]phosphinic acid ethyl ester were dissolved in 1 ml of dichloromethane and the solution was stirred at room temperature for 3 hours in the presence of 1 ml of bromotrimethylsilane and 0.1 ml of trifluoroacetic acid. The solvent was removed by evaporation and the residue was treated three times with acetone/water (9:1) and the solvent was removed by evaporation each time. Finally, the product was triturated with diethyl ether to yield 55 mg of [(2,5-dioxo-1-imidazolidinyl)-methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a foam.

Example 29

In an analogous manner to that described in Example 4(B),
from [[1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl]methyl][)RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl]methyl[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a pale yellow foam;
from [[1,4-dihydro-2,4-dioxo-2(2H)-quinazolinyl]methyl][(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[1,4-dihydro-2,4-dioxo-3-(2H)-quinazolinyl]methyl][(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]-phosphinic acid in the form of an off-white foam;
from [[2,4-dioxo-2H-1,3-benzoxazin-3(4H)-yl]methyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[2,4-dioxo-2H-1,3-benzoxazin-3(4H)-yl)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl] carbamoyl)pentyl]phosphinic acid in the form of an off-white foam;
from [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][[3,5-dioxo-4H-thieno[3,4-c]pyrrol-5(6H)-yl]methyl]phosphinic acid ethyl ester there was obtained [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][[3,5-dioxo-4H-thieno[3,4-c]pyrrol-5(6H)-yl]methyl]phosphinic acid in the form of a cream foam;
from [[1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid in the form of a white foam;
from [(4-amino-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid methyl ester there was obtained [(4-amino-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid in the form of an orange foam;
from [(4-amino-3-bromo-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-amino-3-bromo-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid in the form of a yellow foam;
from [(4-amino-3-chloro-1,8-naphthalenedicarboximido) methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-amino-3-chloro-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-

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pentyl]phosphinic acid in the form of a yellow powder;
from [(4-amino-3-jodo-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-amino-3-jodo-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid in the form of an orange-yellow powder;
from [(3-amino-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3-amino-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid in the form of an orange foam;
from [(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl][(1,8-naphthalenedicarboximido)-methyl]phosphinic acid ethyl ester there was obtained [(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]-carbamoyl]pentyl][(1,8-naphthalenedicarboximido)methyl]phosphinic acid in the form of a white powder;
from [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][[1,3,6,7-tetrahydro-1,3-dioxo-2H-indeno[6,7,1-def]isoquinolin-2-yl]methyl]phosphinic acid ethyl ester there was obtained [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][[1,3,6,7-tetrahydro-1,3-dioxo-2H-indeno-[6,7,1-def] isoquinolin-2-yl]methyl]phosphinic acid in the form of a pale cream foam;
from [(3,6-dinitro-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3,6-dinitro-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid in the form of a white foam;
from [(4-amino-3-bromo-1,8-naphthalenedicarboximido)methyl][(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-amino-3-bromo-1,8-naphthalenedicarboximido)methyl][(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]-pentyl]phosphinic acid in the form of a yellow powder of melting point 277-280°C (decomposition);
from [[6-amino-5-bromo-1H-benz[d,e]isoquinolin-2(3H)-yl]methyl][(R or S)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[6-amino-5-bromo-1H-benz[d,e]isoquinolin-2(3H)-yl]methyl[(R or S)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid in the form of a yellow powder;
from [(3-bromo-1,8-naphtalenedicarboximido)methyl][(R or S)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3-bromo-1,8-naphtalenedicarboximido)methyl][(R or S)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid in the form of a white powder;
from [(3,6-diamino-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3,6-diamino-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid trifluoracetate in the form of an orange foam;
from [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(4-nitro-1,8-naphthalenedicarboximido)methyl]phosphinic acid ethyl ester there was obtained [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(4-nitro-1,8-naphthalenedicarboximido)methyl]phosphinic acid in the form of an off-white foam;
from [(2-amino-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(2-amino-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid in the form of an orange foam;
from [(4-benzyloxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-benzyloxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid in the form of an off-white foam;
from [(4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl] carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a pale yellow foam;
from [(3,6-diacetamido-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3,6-diacetamido-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid in the form of a pale yellow foam;
from [(3,6-dihydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3,6-dihydroxy-

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1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]carbamoyl]-pentyl]phosphinic acid in the form of a yellow foam;
from [(3-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]carbamoyl]pentyl]-phosphinic acid in the form of a yellow foam;
from [(4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]-carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]-phosphinic acid in the form of a yellow solid of melting point 230-231°C;
from [(4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]carbamoyl]pentyl]-phosphinic acid in the form of a yellow powder of melting point 185-193°C;
from [(3-hydroxy-4-nitro-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3-hydroxy-4-nitro-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]-carbamoyl]pentyl]phosphinic acid in the form of a yellow foam;
from [(3-bromo-4-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3-bromo-4-hydroxy1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]-carbamoyl]pentyl]phosphinic acid in the form of a yellow solid;
from [(3-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]-carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]-phosphinic acid in the form of a hygroscopic powder of melting point >250°C;
from [(3-bromo-4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3-bromo-4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]-phosphinic acid in the form of a pale yellow solid of melting point 251-252°C; and
from [(3,6-dihydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3,6-dihydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]-phosphinic acid in the form of a pale yellow powder of melting point 280-282°C.

Example 30

In an analogous manner to that described in Example 10,
from [[[N-[1-[(benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[[N-[1-[(benzyloxy)-carbonyl]-L-prolyl]-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[R orS)-2-oxo-3-azacyclotridecyl]carbamoyl]-pentyl]phosphinic acid in the form of a white foam;
from [(R)-1-[[N-[1-[(benzyloxy)carbonyl[-L-prolyl]-D-leucyl]amino]methyl][(RS)-4-methyl-2-[[R or S)-3methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester thre was obtained [(R)-1-[[N-[1-[-(benzyloxy)carbonyl[-L-prolyl]-D-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butylcarbamoyl]pentyl]phosphinic acid in the form of a white foam;
from [(S)-1-[[N-[1-[(benzyloxy)carbonyl[-L-prolyl]-D-leucyl]amino]ethyl][(RS)-4-methyl-2-[[(S)-2-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(S)-1-[[N-[1-[-(benzyloxy)carbonyl]-L-prolyl]-D-leucyl]amino]ethyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam;
from [[(S)-3-[1-(benzyloxy)formamido]-2,5-dioxo-1-pyrrolidinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[(S)-3-[1-(benzyloxy)formamido]-2,5-dioxo-1-pyrrolidinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam;
from [[(R)-3-[1-(benzyloxy)formamido]-2,5-dioxo-1-pyrrolidinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[(R)-3-[1-(benzyloxy)formamido]-2,5-dioxo-1-pyrrolidinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-

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butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam;
from [[(S)-3-[1-(benzyloxy)carbonyl]-L-prolyl]amino]-2,5-dioxo-1-pyrrolidinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[(S)-3-[1-(benzyloxy)carbonyl]-L-prolyl]amino]-2,5-dioxo-1-pyrrolidinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam;
from [[(R)-3-[[1-[(benzyloxy)carbonyl]-L-prolyl]amino]-2,5-dioxo-1-pyrrolidinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl] pentyl]phosphinic acid ethyl ester there was obtained [[(R)-3-[[1-[(benzyloxy)carbonyl]-L-prolyl]amino]-2,5-dioxo-1-pyrrolidinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam;
from [[[[3,4-dihydro-1,3-dioxonaphth[1,8-cd]azepin-2(2H)-yl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[3,4-dihydro-1,3-dioxonaphth[1,8-cd]azepin-2(1H)-yl]methyl[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid in the form of a white foam;
from [[(S)-3-[[1-[(benzyloxy)carbonyl]-L-prolyl]amino]-2,6-dioxopiperixino]methyl[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[(S)-3-[-[1-[(benzyloxy)carbonyl]-L-prolyl]amino]-2,6-dioxopiperidino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam;
from [[(R)-3-[[1-[(benzyloxy)carbonyl]-L-prolyl]amino]-2,6-dioxopiperidino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[(R)-3-[-[1-[(benzyloxy)carbonyl]-L-prolyl]amino]-2,6-dioxopiperidino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam; and
from [(1,3-dihydro-1,3-dioxo-2H-dibenz[e,g]isoindol-2-yl)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid isopropyl ester there was obtained [(1,3-dihydro-1,3-dioxo-2H-dibenz[e,g]isoindol-2-yl)methyl][(RS)-4-methyl-2-[[(S) -3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid in the form of a white foam.

Example 31

In an analogous manner to that described in Example 25(B),
from [(4-chloro-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-chloro-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid in the form of an off-white foam;
from [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(1,2-napththalenedicarboximido)methyl]phosphinic acid ethyl ester there was obtained [(RS)-4-methyl-1-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(1,2-napththalenedicarboximido)methyl]phosphinic acid in the form of an off-white foam;
from [(3-bromo-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3-bromo-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl]butyl]carbamoyl]pentyl]-phosphinic acid in the form of a white foam;
from [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(3-nitro-1,8-napthalenedicarboximido)methyl]phosphinic acid ethyl ester there was obtained [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][(3-nitro-1,8-naphthalenedi carboximido)methyl]phosphinic acid in the form of an off-white foam;
from [(2-methoxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(2-methoxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid in the form of an off-white foam;
from [(3,4-dihydro-1,3-dioxo-2(1H)-isoquinolinyl)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)-butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(3,4-dihydro-1,3-dioxo-2(1H)-isoquinolinyl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of an off-white foam;
from [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][[1,3-dioxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl]phosphinic acid ethyl ester there was obtained [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][[1,3-dioxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl]methyl]phosphinic acid hydrobromide in the form of a yellow foam;

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from [(3,4-dihydro-1,3-dioxo-2(1H)-isoquinolinyl)from[[1,3-dioxo-1H-pyrrolo[3,4-b]pyridin-2(3H)-yl]methyl[-(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(1,3-dioxo-1H-pyrrolo[3,4-b]pyridin-2(3H)-yl]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of an yellow-brown foam; and from [(4-methoxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-methoxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid in the form of a pale yellow foam.

Example 32

In an analogous manner to that described in Example 28(B), from [(4-acetamido-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [(4-acetamido-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[-(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a yellow-green foam.

Example 33

In an analogous manner to that described in Example 1(B),
from [[(S)-3-acetamidosuccinimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[(S)-3-acetamidosuccinimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam; and
from [[(R)-3-acetamidosuccinimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid ethyl ester there was obtained [[(R)-3-acetamidosuccinimido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phos phinic acid in the form of a white foam.

Example 34

A solution of 0.2 g of [(4-amino-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in 2 ml of glacial acetic acid was treated with two drops of bromine. The solution was stirred at room temperature for 30 minutes and then evaporated under reduced pressure. After a further four evaporations from 10 ml of methanol each time there were obtained 230 mg of [(4-amino-3-bromo-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a yellow powder.

Example 35

A solution of 0.075 g of [(4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in 17 ml of glacial acetic acid was treated with 10 drops of bromine and the mixture was left to stand at room temperature for 3 days. The solvent was then removed by evaporation and the residue was treated with 20 ml of toluene and re-evaporated. This procedure was repeated 5 times and the product was finally taken up in 20 ml of methanol/dichloromethane (1:1) and re-evaporated to give 0.085 g of [(3-bromo-4-hydroxy-1,8-naphthalenedicarboximido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid in the form of a yellow foam.

Example 36

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(A) The preparation of the starting material:

(i) In a manner analogous to that described in Example 9(A)(i) and (ii), but starting with (aminomethyl)[-(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester acetate [prepared as described in Example 20(A)(iii)] there was obtained benzyl(S)-2-[[(S)-1-[[[ethoxy[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinyl]methyl]carbamoyl]-3-methylbutyl]carbamoyl]-1-pyrrolidinecarboxylate in the form of a white foam.

(ii) 0.36 g of benzyl(S)-2-[[(S)-1-[[[ethoxy[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinyl]methyl]carbamoyl]-3-methylbutyl]carbamoyl]-1-pyrrolidinecarboxylate was dissolved in 5 ml of ethanol containing 0.5 ml of 1M hydrochloric acid. The solution was hydrogenated over 5% palladium-on-charcoal for 2 hours. After filtration and evaporation of the filtrate the residue was re-evaporated with toluene until a white solid was obtained. This solid was dissolved in 6 ml of dichloromethane, the solution was cooled to 0°C and treated with 0.15 ml of triethylamine and 0.064 ml of benzoyl chloride. The mixture was stirred at room temperature for 16 hours and the solvent was then removed by evaporation. The residue was dissolved in ethyl acetate, the mixture was filtered and the filtrate was evaporated to give a pale yellow gum. Chromatography on silica gel using 3% ethanol in chloroform for the elution followed by evaporation yielded 0.32 g of [[N[(1-benzoyl-L-prolyl)-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester in the form of a white foam.

(B) The process:

-0.25 g of [[[N-(1-benzoyl-L-prolyl)-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester was dissolved in a mixture of 1 ml of acetic acid and 1 ml of 45% hydrogen bromide in acetic acid and the mixture was left to stand at room temperature overnight. The solution was treated with diethyl ether, the precipitated gum was allowed to settle and the ethereal solution was removed by decantation. Further treatment with diethyl ether followed by dichloromethane and subsequent drying in a high vacuum yielded 0.17 g of [[[N-(1-benzoyl-L-prolyl)-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a light brown foam containing some hydrogen bromide.

Example 37

(A) The preparation of the stating material:

In a manner analogous to that described in Example 36(A), but using trifluoroacetic anhydride in place of benzoyl chloride, there was obtained [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl][[[N-[1-trifluoroacetyl)-L-prolyl]-L-leucyl]amino]methyl]phosphinic acid ethyl ester in the form of a pale yellow foam.

(B) The process:

[(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][[[N-[1-trifluoroacetyl)-L-prolyl]-L-leucyl]amino]methyl]phosphinic acid ethyl ester was treated in a manner analogous to that described in Example 36(B) to give [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl][[[N-[1-trifluoroacetyl) -L-prolyl]-L-leucyl]amino]methyl]phosphinic acid in the form of a pale brown solid containing some hydrogen bromide.

Example 38

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(A) The preparation of the starting material:

0.65 g of [[[N-[1-[(benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester was dissolved in 8 ml of acetic acid, 2 ml of acetaldehyde were added and the mixture was hydrogenated for 4 hours over 0.01 g of 5% palladium-on-charcoal. The solution was filtered and the filtrate was evaporated to dryness.

(B) The process:

The product obtained according to paragraph (a) was dissolved in 2 ml of 45% hydrogen bromide in acetic acid and left to stand at room temperature overnight. The solution was evaporated and the residue was re-evaporated with toluene until a pale brown solid was obtained. This solid (0.6 g) was precipitated from methanolic solution by the addition of diethyl ether and was then dried in a high vacuum to yield [[N-(1-ethyl-L-prolyl)-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid in the form of a brown foam.

Example 39

0.55 g of [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][[(N-L-prolyl-L-leucyl)amino]methyl]phosphinic acid ethyl ester was dissolved in 4 ml of acetic acid and 2 ml of 45% hydrogen bromide in acetic acid and the mixture was left to stand at room temperature overnight. The solvent was removed by evaporation and the residue was re-evaporated with toluene to give 0.47 g of a pale brown foam. Precipitation from methanolic solution by the addition of diethyl ether and drying in a high vacuum yielded [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl][[(N-L-prolyl-L-leucyl)amino]methyl]phosphinic acid in the form of a brown foam.

Example 40

(A) The preparation of starting material:

In a manner analogous to that described in Example 9(A)(i) und (ii), but starting with (aminomethyl)[-(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester and using N^2-[(benzyloxy)carbonyl]-N^6-phthaloyl-L-lysine in place of N-[(benzyloxy)carbonyl]-L-proline, there was obtained [[[N-[(S)-2-[1-(benzyloxy)formamido]-6-phthalimidohexanoyl]-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester in the form of a white foam,.

(B) The process:

0.6 g of [[[N-[(S)-2-[1-(benzyloxy)formamido]-6-phthalimidohexanoyl]-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester was dissolved in 2 ml of acetic acid and 2 ml of 45% hydrogen bromide in acetic acid and left to stand at room temperature overnight. The solvent was removed by evaporation and the residue was re-evaporated with toluene until a solid was obtained. This solid was dissolved in aqueous potassium hydrogen carbonate solution, 0.14 ml of benzyl chloroformate was added and the mixture was stirred for 4 hours. The solution was extracted twice with diethyl ether and acidified with hydrochloric acid. The solid was separated and dissolved by extraction with hot chloroform. The organic solution was dried over anhydrous magnesium sulphate and evaporated to yield 0.53 g of [[[N-[(S)-2-[1-(benzyloxy)formamido]-6-phthalimidohexanoyl]-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of an amorphous cream powder.

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Example 41

In a manner analogous to that described in Example 39, there was obtained [[[N-[N-[(benzyloxy)-carbonyl]-L-alanyl[-L-leucyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl]phosphinic acid in the form of a pale brown powder.

Example 42

(A) The preparation of the starting material:

In a manner analogous to that described in Example 36(A)(i), but using N-(benzyloxy)carbonyl-L-alanine in place of N-(benzyloxy)carbonyl-L-leucine there was obtained [[[N-[1-[(benzyloxy)carbonyl]-L-prolyl]-L-alanyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester in the form of a foam.

(B) The process:

[[[N-[1-[(benzyloxy)carbonyl]-L-prolyl]-L-alanyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester was treated in a similar manner to that described in Example 39(B) to yield [[[N-[1-[(benzyloxy) carbonyl]-L-prolyl]-L-alanyl]amino]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid in the form of a white foam.

Example 43

(A) The preparation of the starting material:

In a manner analogous to that described in Example 41(A) there was obtained [[[(S)-2-[1-[(benzyloxy)-carbonyl]-L-prolyl]amino]-6-phthalimidohexanamido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester.

(B) The process:

[[[(S)-2-[1-[(benzyloxy)carbonyl]-L-prolyl]amino]-6-phthalimidohexanamido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid ethyl ester was treated in a similar manner to that described in Example 39(B) to give [[[(S)-2-[1-[(benzyloxy)carbonyl]-L-prolyl]amino]-6-phthalimidohexanamido]methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]-phosphinic acid in the form of a foam.

Example 44

(A) The preparation of the starting material:

(i) 21.0 g of N^6-[(benzyloxy)carbonyl]-L-lysine were dissolved in 75 ml of 2M sodium hydroxide solution and 75 ml of dioxane. 18.0 g of di-tert.butyl dicarbonate were added and the mixture was stirred at room temperature for 16 hours. The solution was evaporated in order to remove dioxane, water was added, the solution was extracted with diethyl ether and acidified with 6M hydrochloroic acid. The product was taken up in ethyl acetate, washed with sodium chloride solution, dried over magnesium sulphate and evaporated to give an oil. A solution of this oil in tetrahydrofuran was cooled to -15°C and treated with 8.51 ml of N-ethylmorpholine, 8.61 ml of isobutylchloroformate and, after 5 minutes with 10.0 ml of a 40% aqueous solution of methylamine. After stirring at 0°C for 2 hours the solvent was removed by evaporation and the residue was dissolved in ethyl acetate. The organic solution was washed with water, 5% citric acid solution, water, 5% sodium hydrogen carbonate solution and sodium chloride solution, dried over anhydrous

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magnesium sulphate and evaporated. Recrystallization from ethyl acetate yielded 20.5 g of N^6-[(benzyloxy)-carbonyl]-N^2-(tert.-butoxycarbonyl)-L-lysine methylamide in the form of a white solid of melting point 100-102°C.

(ii) 5.7 g of (R or S)-2-[[ethoxy(phthalimidomethyl)phosphinyl]methyl]-4-methylvaleric acid were dissolved in tetrahydrofuran and cooled to -20°C. 1.90 ml of N-ethylmorpholine and 1.97 ml of isobutyl chloroformate were added and, after stirring at -20°C for 20 minutes, 2.4 g of N-hydroxybenzotriazole were added. The mixture was then stirred at -20°C for 20 minutes. A solution of N^6-[(benzyloxy)carbonyl]-L-lysine methylamide hydrochloride (prepared by treating 5.91 g of N^6[(benzyloxy)carbonyl[-N^2-(tert.-butoxycarbonyl)-L-lysine methylamide with 4M hydrogen chloride in dioxane for 30 minutes at room temperature followed by evaporation and trituration with diethyl ether) in dimethylformamide was neutralized with 1.90 ml of N-ethylmorpholine and added to the mixed anhydride solution prepared as described above. The mixture was stirred at 0°C for 1 hour, left to stand at room temperature overnight and then evaporated. The residue was taken up in dichloromethane, washed with water, 1M hydrochloric acid, water, 5% sodium hydrogen carbonate solution and sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated to give an oil. Chromatography on silica gel using 4% methanol in chloroform for the elution yielded 6.8 g of benzyl [(S)-5-[(R or S)-2-[[ethoxy(phthalimidomethyl)phosphinyl]methyl]-4-methylvalerimido]-5-(methylcarbamoyl)pentyl]carbamate in the form of an oil.

(iii) 6.56 g of benzyl [(S)-5-[(R or S)-2-[[ethoxy(phthalimidomethyl)phosphinyl]methyl]-4-methylvalerimido]-5-(methylcarbamoyl)pentyl]carbamate were dissolved in a mixture of 120 ml of ethanol and 1.96 ml of hydrazine hydrate, the mixture was stirred for 16 hours and then evaporated. Traces of hydrazine hydrate were removed by the addition and evaporation of ethanol followed by toluene. The residue was suspended in dichloromethane and acidified with acetic acid. The mixture was stirred at room temperature for 30 minutes, filtered and the filtrate was evaporated. The residue was taken up in 5% citric acid solution, extracted with diethyl ether, filtered, the filtrate was made basic by the addition of solid sodium hydrogen carbonate and the product was extracted three times with 20 ml of dichloromethane each time. The solution was dried over magnesium sulphate and evaporated to 20 ml, 2.82 g of 1,8-naphthalic anydride were added and the solution was stirred at room temperature for 16 hours. 1.17 g of N-hydroxybenzotriazole and 1.61 g of N,N'-dicyclohexylcarbodiimide were added to the solution at 9°C. The solution was stirred at 0°C for 2 hours, filtered, the filtrate was washed with 5% sodium hydrogen carbonate solution, dried over anhydrous magnesium sulphate and evaporated to give an oil. Chromatography on silica gel using 4% methanol in dichloromethane for the elution yielded 4.0 g of benzyl [(S)-5-[(R or S)-2-[[ethoxy-[(1,8-naphthalenedicarboximido)methyl]phosphinyl] methyl]-4-methylvaleramido]-5-(ethylcarbamoyl)pentyl]-carbamate in the form of a white foam.

(iv) 1.0 g of benzyl [(S)-5-[(R or S)-2-[[ethoxy[(1,8-naphthalenedicarboximido)methyl]phosphinyl]methyl]-4-methylvaleramido]-5-(ethylcarbamoyl)pentyl]carbamate in ethanol containing 1.4 ml of 1M hydrochloric acid was hydrogenated for 5 hours over 5% palladium-on-charcoal. The catalyst was removed by filtration and the filtrate was evaporated to dryness. Final traces of ethanol were removed by 2-fold re-evaporation with 15 ml of toluene each time. The residue was taken up in dichloromethane, cooled to 0°C, neutralized with 0.18 ml of N-ethylmorpholine and treated with 0.293 g of N-[(benzyloxy)carbonyl]-glycine, 0.227 g of hydroxybenzotriazole and 0.316 g of N,N'-dicyclohexylcarbodiimide. The mixture was stirred at 0°C for 1 hour, left to stand at 4°C overnight, filtered, the filtrate was washed with 5% citric acid, water, 5% sodium hydrogen carbonate solution and sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated. Chromatography on silica gel using 7.5% methanol in ethyl acetate for the elution yielded 0.51 g of benzyl [[[(S)-5-[(R or S)-2-[[ethoxy[(1.8-naphthalenedicarboximido)methyl]phosphinyl]methyl]-4-methyl-valeramido)-5-(methylcarbamoyl)pentyl]carbamoyl]methyl]carbamate in the form of a foam.

(B) The process:

0.1 g of benzyl [[[(S)-5-[(R or S)-2-[[ethoxy[(1,8-naphthalenedicarboximido)methyl]phosphinyl]methyl]-4-methylvaleramido]-5-(methylcarbamoyl)pentyl]carbamoyl]methyl]carbamate in 3 ml of 45% hydrogen bromide in acetic acid was left to stand at room temperature for 16 hours. The mixture was evaporated and the residue was re-evaporated three times with 10 ml of toluene each time. Precipitation from methanol/diethyl ether followed by lyophilization from water yielded 0.11 g of [(R or S)-2-[[(S)-5-(glycylamino)-1-(methylcarbamoyl)pentyl]carba moyl]-4-methylpentyl][(1,8-naphthalenedicarboximido)methyl]phosphinic acid hydrobromide in the form of a white freeze dried solid.

The (R or S)-2-[[(ethoxy)(phthalimidomethyl]phosphinyl]methyl]-4-methylvaleric acid used in paragraph (A)(ii) was prepared as follows

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(A) A vigorously stirred mixture of 17.6 g (0.27 mol) of crystalline phosphinic acid and 43.6 g (0.2 mol) of benzyl 2-isobutylacrylate in 400 ml of dichloromethane was cooled to 0°C and treated dropwise with 53.4 g (0.53 mol) of triethylamine while maintaining the temperature at below 5°C. After completion of the addition a solution of 56.0 g (0.52 mol) of trimethylsilyl chloride in 100 ml of dichloromethane was added while stirring vigorously and maintaining the temperature at 10-12°C. After 30 minutes the cooling bath was removed and the mixture was stirred at room temperature for 24 hours. The mixture was then treated with 200 ml of water and 30 ml of 10% suphuric acid. The organic phase was separated and washed with 200 ml of saturated sodium chloride solution. The combined aqueous extracts were re-extracted with 100 ml of dichloromethane and the organic phase was washed with 100 ml of sodium chloride solution and added to the previously obtained dichloromethane extracts. After drying over anhydrous sodium sulphate the dichloromethane was removed by evaporation to give 59.2 g of [(RS)-2-[(benzyloxy)carbonyl]-4-methylpentyl]phosphinic acid in the form of a colourless oil.

(b) The compound prepared in the preceding paragraph was dissolved in 600 ml of ethyl acetate, 25.0 g of S(-)-α-methylbenzylamine were added and the solution was left to crystallize for 24 hours. The crystalline salt was collected by filtration and dried to give 34.0 g of a white solid which was recrystallized overnight from a mixture of 120 ml of ethanol and 48 ml of ethyl acetate. The solid was collected and dried to give 21.3 g of a crystalline salt which was recrystallized overnight from a mixture of 120 ml of ethanol and ethyl acetate. There were obtained 16.8 g of [(R or S)-2-[(benzyloxy)carbonyl]-4-methylpentyl]phosphinic acid S(-)-α-methylbenzylamine salt in the form of white crystals of melting point 137-138°C and $[\alpha]_{589}^{20}$ = -8.9° (c = 5% in ethanol).

(c) A suspension of 5.8 g of the salt prepared as described in the preceding paragraph in 100 ml of ethyl acetate was shaken with 100 ml of 10% sulphuric acid until a clear solution was obtained. The organic layer was separated, washed with 100 ml of saturated sodium chloride solution and dried over anhydrous sodium sulphate. After evaporation there were obtained 4.0 g of [(R or S)-2-[(benzyloxy)carbonyl]-4-methylpentyl]phosphinic acid in the form of a colourless oil; $[\alpha]_{589}^{20}$ = -12.3° (c = 5% in ethanol).

(d) 4.0 g of the compound prepared in the preceding paragraph were dissolved in 40 ml of dry tetrahydrofuran containing 0.7 ml of ethanol. 3.1 g of N,N'-dicyclohexylcarbodiimide and 0.17 g of 4-dimethylaminopyridine were added and the mixture was stirred at room temperature for 18 hours. The solvent was then removed by evaporation, the residue was triturated with 50 ml of ethyl acetate and the dicyclohexylurea was removed by filtration. The filtrate was washed with 50 ml of 5% potassium hydrogen sulphate solution and then with 50 ml of saturated sodium hydrogen carbonate solution. After drying over anhydrous sodium sulphate the ethyl acetate was removed by evaporation to give 4.5 g of benzyl (R or S)-2-[(ethoxyphosphinyl)methyl]-4-methylvalerate in the form of a colourless oil; $[\alpha]_{589}^{20}$ = -8.5° (c = 5% in ethanol.

(e) A mixture of 4.5 g of benzyl (R or S)-2-[(ethoxyphosphinyl)methyl]-4-methylvalerate and 1.8 g of diisopropylethylamine in 30 ml of dichloromethane was cooled in an ice-bath while stirring under nitrogen. 7 ml of bis(trimethylsilyl)acetamide were added, the mixture was stirred for 5 minutes and then 3.36 g of N-bromomethylphthalimide were added. The cooling bath was removed and the mixture was left to come to room temperature. After stirring for a further 5 hours the solution was washed with 50 ml of 10% sulphuric acid and 50 ml of sodium chloride solution, dried over anhydrous sodium sulphate and evaporated to give 6.6 g of a yellow oil which was purified by flash chromatography on silica gel using ethyl acetate/n-hexane (3:1) for the elution. There were obtained 4.5 g of benzyl (R or S)-2-[[(ethoxy)(phthalimidomethyl)-]phosphinyl]methyl]-4-methylvalerate in the form of a colourless oil.

(f) 4.5 g of benzyl (R or S)-2-[[(ethoxy)(phthalimidomethyl)phosphinyl]methyl]-4-methylvalerate were dissolved in 120 ml of ethanol and the solution was hydrogenated over 1.6 g of 10% palladium-on-charcoal for 5.5 hours. After filtration and evaporation of the filtrate there were obtained 3.0 g of (R or S)-2-[[(ethoxy)-(phthalimidomethyl)phosphinyl]methyl]-4-methylvaleric acid in the form of a white foam.

The following Examples illustrate pharmaceutical preparations containing the compounds provided by the present invention:

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Example A

Tablets containing the following ingredients may be produced in a conventional manner:

Ingredient	Per tablet
Compound of formula I	10.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg
Tablet weight	215.0 mg

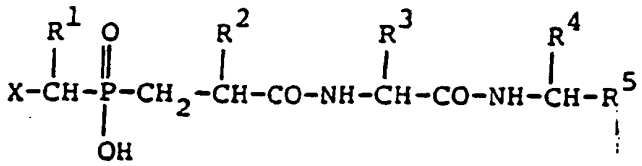
Example B

Capsules containing the following ingredients may be produced in a conventional manner:

Ingredient	Per capsule
Compound of formula I	10.0 mg
Lactose	165.0 mg
Maize starch	20.0 mg
Talc	5.0 mg
Capsule fill weight	200.0 mg

Claims

1. Compounds of the general formula



I

wherein
R^1 represents a hydrogen atom or a C_1-C_6-alkyl or aryl-(C_1-C_6-alkyl) group;
R^2 represents a C_2-C_5-alkyl group;
R^3 represents the side-chain of a natural α-amino acid in which any functional group present is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, with the proviso that R^3 does not represent a hydrogen atom or a methyl group;
R^4 represents a hydrogen atom or a methyl group; or
R^3 and R^4 together represent a group of the formula $-(CH_2)_n-$ in which n stands for a number from 4 to 11 inclusive;
R^5 represents a hydrogen atom or a C_1-C_6-alkyl, carboxyl, C_1-C_6-alkoxycarbonyl or C_1-C_6-alkylaminocarbonyl group; and

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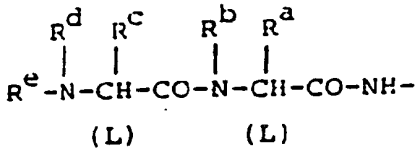
X represents either a cyclic imido group derived from an aliphatic or aromatic dicarboxylic acid, from an N-carboxyamino acid, from an azadicarboxylic acid or from an O-carboxyhydroxy acid or a group of the formula



(a)

in which R^a represents the side-chain of a natural α-amino acid in which any functional group present is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, R^b represents a hydrogen atom or R^a and R^b together represent a trimethylene group, R^c represents the side-chain of a natural α-amino acid in which any functional group is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, R^d represents a hydrogen atom or R^c and R^d together represent a trimethylene group and R^e represents a protecting group or an acyl, C_1-C_6-alkyl-sulphonyl or arylsulphonyl group.

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein R^1 represents a hydrogen atom or a C_1-C_6-alkyl group.

3. Compounds according to claim 2, wherein R^1 represents a hydrogen atom or a methyl group.

4. Compounds according to any one of claims 1 to 3, wherein R^2 represents a C_3-or C_4-alkyl group.

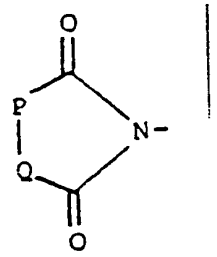
5. Compounds according to claim 4, wherein R^2 repreesents a n-propyl, isobutyl of sec-butyl group.

6. Compounds according to any one of claims 1 to 5, wherein R^3 represents an isobutyl group, R^4 represents a hydrogen atom or R^3 and R^4 together represents a group of the formula $-(CH_2)_n-$ in which n stands for a number from 5 to 9 inclusive and R^5 represents a hydrogen atom.

7. Compounds according to any one of claims 1 to 5, wherein R^3 represents an isobutyl group, R^4 represents a methyl group and R^5 represents a carboxyl or C_1-C_6-alkoxycarbonyl group.

8. Compounds according to claim 7, wherein R^5 represents a carboxyl or ethoxycarbonyl group.

9. Compounds according to any one of claims 1 to 8, wherein X represents a cyclic imido group of the formula



(b)

wherein P and Q together represent a group of the formula
$-CH(R^f)-CH(R^f)-$,
$-CH(R^f)-CH(R^f)-CH(R^f)-$,
$-O-CH(R^f)-$,
$-N(R^f)-CH(R^f)-$,
$-N(R^f)-N(R^f)-$,
$-N=N-$ or
$-C(R^f)=C(R^f)-$,
in which each R^f represents a hydrogen atom or a C_1-C_6-alkyl, aryl, aryl-(C_1-C_6-alkyl), or C_1-C_6-alkanoylamino group or an acylamino group in which the acyl moiety is derived from a naturally occurring α-amino acid in which the amino group is optionally protected,
or P and Q together represent an optionally substituted aromatic system in which the optional substitution comprises one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, hydroxy, aryl-(C_1-C_6-alkoxy), nitro, amino, C_1-C_6-alkanoylamino, mono(C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino and C_1-C_6-alkylsulphonylamino.

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10. Compounds according to claim 9, wherein each R^f represents a hydrogen atom of a C_1-C_6-alkyl or C_1-C_6-alkanoylamino group.

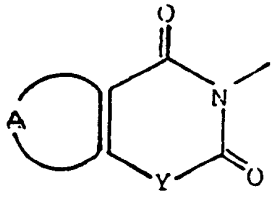
11. Compounds according to claim 10, where P and Q together represent a group of the formula $-C(R^f)-=C(R^f)-$ in which one R^f represents an aryl group and the other R^f represents a hydrogen atom or an aryl group.

12. Compounds according to claim 11, wherein one R^f represents a phenyl group and the other R^f represents a hydrogen atom or a phenyl group.

13. Compounds according to claim 9, wherein P and Q together represent a 1,2-phenylene or 2,3-naphthylene group which is optionally substituted by one or more substituents selected from C_1-C_6-alkoxy, halogen, hydroxy, amino and C_1-C_6-alkanoylamino.

14. Compounds according to claim 9, wherein P and Q together represent a 1,8-naphthylene group which is optionally substituted by a C_1-C_6-alkoxy, hydroxy or amino group.

15. Compounds according to any one of claims 1 to 8, wherein X represents a cyclic imido group of the formula



(c)

wherein A represents the residue of an optionally substituted aromatic system in which the optional substitution comprises one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, hydroxy, aryl-(C_1-C_6-alkoxy), nitro, amino, C_1-C_6-alkanoylamino, mono(C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino and C_1-C_6-alkylsulphonylamino and Y represents -O-, -NH- or $-NR^g-$ in which R^g represents hydrogen or C_1-C_6-alkyl.

16. Compounds according to claim 15, wherein A represents the residue of a benzene ring and Y represents $-NR^g-$.

17. Compounds according to any one of claims 1 to 8, wherein X represents a group of formula (a) in which R^a represents the side-chain of a natural α-amino acid in which any functional group present is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated and R^b represents a hydrogen atom, R^c and R^d together represent a trimethylene group and R^e represents a protecting group or an acyl group.

18. Compounds according to claim 17, wherein R^a represents an isobutyl group.

19. Compounds according to claim 17 or claim 18, wherein R^e represents a benzyloxycarbonyl or acetyl group.

20. [(3-Aminophthalimido)methyl][(RS)-4-methyl-2-[[(S)3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]-pentyl]phosphinic acid.

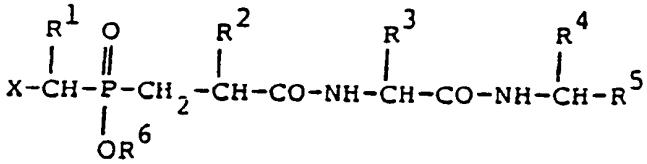
21. [(RS)-4-Methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid.

22. [(R or S)-4-Methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid.

23. N-[N-[(R or S)-2-[[[[[N-[1-(Benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl]hydroxyphosphinyl]-methyl]-4-methylvaleryl]-L-leucyl]-L-alanine.

24. [[1,4-Dihydro-2,4-dioxo-3(2H)-quinazolinyl]methyl][[(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid.

25. Compounds of the general formula



II

wherein R^1, R^2, R^3, R^4, R^5 and X have the significance given in claim 1 and R^6 represents a C_1-C_6-alkyl group.

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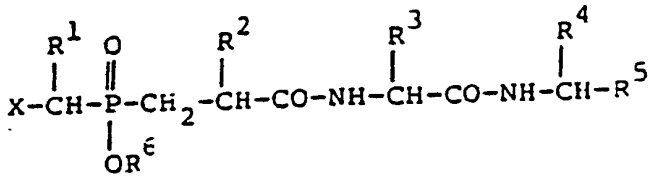
26. Compounds according to any one of claim 1 to 24 and pharmaceutically acceptable salts thereof for use as therapeutically active substances.

27. Compounds according to any one of claims 1 to 24 and pharmaceutically acceptable salts thereof for use as collagenase inhibitors.

28. A process for the manufacture of the compounds of formula I given in claim 1 and pharmaceutically acceptable salts thereof, which process comprises treating a compound of the general formula



II

wherein R^1, R^2, R^3, R^4, R^5 and X have the significance given in claim 1 and R^6 represents a C_1-C_6-alkyl group.
with an acid or with a halotrimethylsilane, if desired functionally modifying a reactive substituent present on a cyclic imide group denoted by X in a compound of formula I obtained and, also if desired, converting a compound of formula I obtained into a pharmaceutically acceptable salt.

29. A medicament containing a compound according to any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier material.

30. A medicament for the control or prevention of degenerative joint diseases, said medicament containing a compound according to any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof and a thereapeutically inert carrier material.

31. A process for the manufacture of a medicament, especially a medicament for the control or prevention of degenerative joint diseases, which process comprises mixing a compound according to any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof and, if desired, one or more other therapeutically active substances with a therapeutically inert carrier material and bringing the mixture into a galenical administration form.

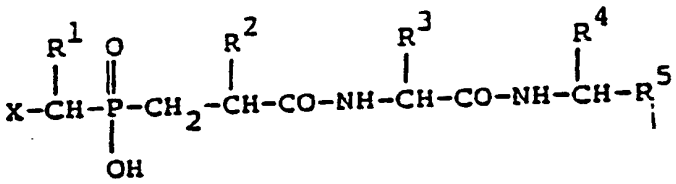
32. The use of a compound according to any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof in the control or prevention of illnesses.

33. The use of a compound according to any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof in the control or prevention of degenerative joint diseases.

34. The use of a compound according to any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the control or prevention of degenerative joint diseases.

Claims for the following contracting state: ES and GR

1. A process for the preparation of compounds of the general formula



I

wherein
R^1 represents a hydrogen atom or a C_1-C_6-alkyl or aryl-(C_1-C_6-alkyl) group;
R^2 represents a C_2-C_5-alkyl group;
R^3 represents the side-chain of a natural α-amino acid in which any functional group present is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, with the proviso that R^3 does not represent a hydrogen atom or a methyl group;
R^4 represents a hydrogen atom or a methyl group; or
R^3 and R^4 together represent a group of the formula $-(CH_2)_n-$ in which n stands for a number from 4 to 11 inclusive;
R^5 represents a hydrogen atom or a C_1-C_6-alkyl, carboxyl, C_1-C_6-alkoxycarbonyl or C_1-C_6-alkylaminocarbonyl

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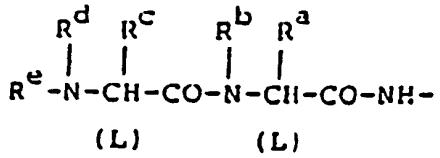
group; and

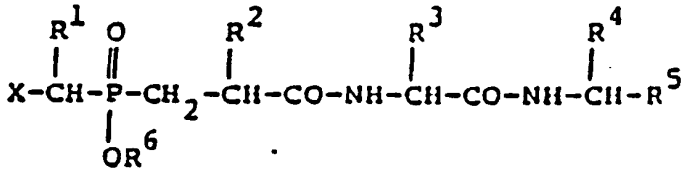
X represents either a cyclic imido group derived from an aliphatic or aromatic dicarboxylic acid, from an N-carboxyamino acid, from an azadicarboxylic acid or from an O-carboxyhydroxy acid or a group of the formula



(a)

in which R^a represents the side-chain of a natural α-amino acid in which any functional group present is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, R^b represents a hydrogen atom or R^a and R^b together represent a trimethylene group, R^c represents the side-chain of a natural α-amino acid in which any functional group is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated, R^d represents a hydrogen atom or R^c and R^d together represent a trimethylene group and R^e represents a protecting group or an acyl, C_1-C_6-alkylsulphonyl or arylsulphonyl group.

and pharmaceutically acceptable salts thereof characterized in that a compound of the general formula



II

wherein R^1, R^2, R^3, R^4, R^5 and X have the significance given in claim 1 and R^6 represents a C_1-C_6-alkyl group.

is treated with an acid or with a halotrimethylsilane, if desired functionally modifying a reactive substituent present on a cyclic imide group denoted by X in a compound of formula I obtained and, also if desired, converting a compound of formula I obtained into a pharmaceutically acceptable salt.

2. A process according to claim 1, wherein R^1 represents a hydrogen atom or a C_1-C_6-alkyl group.

3. A process according to claim 2, wherein R^1 represents a hydrogen atom or a methyl group.

4. A process according to any one of claims 1 to 3, wherein R^2 represents a C_3-or C_4-alkyl group.

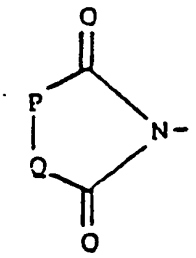
5. A process according to claim 4, wherein R^2 represents a n-propyl, isobutyl or sec-butyl group.

6. A process according to any one of claim 1 to 5, wherein R^3 represents an isobutyl group, R^4 represents a hydrogen atom or R^3 and R^4 together represent a group of the formula $-(CH_2)_n-$ in which n stands for a number from 5 to 9 inclusive and R^5 represents a hydrogen atom.

7. A process according to any one of claims 1 to 5, wherein R^3 represents an isobutyl group, R^4 represents a methyl group and R^5 represents a carboxyl or C_1-C_6-alkoxycarbonyl group.

8. A process according to claim 7, wherein R^5 represents a carboxyl or ethoxycarbonyl group.

9. A process according to any one of claims 1 to 8, wherein X represents a cyclic imido group of the formula



(b)

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wherein P and Q together represent a group of the formula
-CH(R^f)-CH(R^f)-,
-CH(R^f)-CH(R^f)-CH(R^f)-,
-O-CH(R^f)-,
-N(R^f)-CH(R^f)-,
-N(R^f)-N(R^f)-,
-N = N-or
-C(R^f) = C(R^f)-,
in which each R^f represents a hydrogen atom or a C_1-C_6-alkyl, aryl, aryl-(C_1-C_6-alkyl), or C_1-C_6-alkanoylamino group or an acylamino group in which the acyl moiety is derived from a naturally occurring α-amino acid in which the amino group is optionally protected,
or P and Q together represent an optionally substituted aromatic system in which the optional substitution comprises one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, hydroxy, aryl-(C_1-C_6-alkoxy), nitro, amino, C_1-C_6-alkanoylamino, mono(C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino and C_1-C_6-alkylsulphonylamino.

10. A process according to claim 9, wherein each R^frepresents a hydrogen atom of a C_1-C_6-alkyl or C_1-C_6-alkanoylamino group.

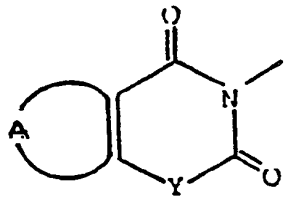
11. A process according to claim 10, where P and Q together represent a group of the formula -C(R^f)-=C(R^f)-in which one R^f represents an aryl group and the other R^f represents a hydrogen atom or an aryl group.

12. A process according to claim 11, wherein one R^frepresents a phenyl group and the other R^f represents a hydrogen atom or a phenyl group.

13. A process according to claim 9, wherein P and Q together represent a 1,2-phenylene or 2,3-naphthylene group which is optionally substituted by one or more substituents selected from C_1-C_6-alkoxy, halogen, hydroxy, amino and C_1-C_6-alkanoylamino.

14. A process according to claim 9, wherein P and Q together represent a 1,8-naphthylene group which is optionally substituted by a C_1-C_6-alkoxy, hydroxy or amino group.

15. A process according to any one of claims 1 to 8, wherein X represents a cyclic imido group of the formula



(c)

wherein A represents the residue of an optionally substituted aromatic system in which the optional substitution comprises one or more substituents selected from C_1C_6-alkyl, C_1-C_6-alkoxy, halogen, hydroxy, aryl-(C_1-C_6-alkoxy), nitro, amino, C_1-C_6-alkanoylamino, mono(C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino and C_1-C_6-alkylsulphonylamino and Y represents -O-, -NH-or -NR^g-in which R^g represents hydrogen or C_1-C_6-alkyl.

16. A process according to claim 15, wherein A represents the residue of a benzene ring and Y represents -NR^g-.

17. A process according to any one of claims 1 to 8, wherein X represents a group of formula (a) in which R^arepresents the side-chain of a natural α-amino acid in which any functional group present is optionally protected or any amino group present is optionally acylated or sulphonylated or any carboxyl group present is optionally amidated and R^b represents a hydrogen atom, R^c and R^d together represent a trimethylene group and R^erepresents a protecting group or an acyl group.

18. A process according to claim 17, wherein R^arepresents an isobutyl group.

19. A process according to claim 17 or claim 18, wherein R^e represents a benzyloxycarbonyl or acetyl group.

20. A process according to claim 1 wherein [(3-aminophthalimido)methyl][(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid is prepared.

21. A process according to claim 1 wherein [(RS)-4-methyl-2-[[(S)-3-methyl-1-(methylcarbamoyl)butyl]-carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl]phosphinic acid is prepared.

22. A process according to claim 1 wherein [(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]-carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid is prepared.

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23. A process according to claim 1 wherein N-[N-[(R or S)-2-[[[[[N-[1-(benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl]hydroxyphosphinyl]methyl]-4-methylvaleryl]-L-leucyl]-L-alanine is prepared.

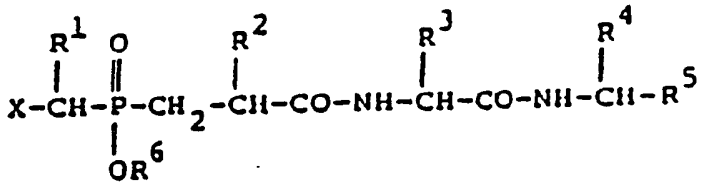
24. A process according to claim 1 wherein [[1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl]methyl][[(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid is prepared.

25. A process for the manufacture of a medicament, especially a medicament for the control or prevention of degenerative joint diseases, which process comprises mixing a compound obtained by a process according to any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof and, if desired, one or more other therapeutically active substances with a therapeutically inert carrier material and bringing the mixture into a galenical administration form.

26. The use of a compound obtained by a process according to any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the control or prevention of illnesses.

27. The use of a compound obtained by a process according to any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the control or prevention of degenerative joint diseases.

28. Compounds of the general formula



II

wherein R^1, R^2, R^3, R^4, R^5 and X have the significance given in claim 1.

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EUROPEAN SEARCH REPORT

Application Number

EP 87 11 8328

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 156 322 (MERCK + CO.) * examples 11, 12, claim 2 *	1	C 07 K 5/06 A 61 K 31/00
A	EP-A-0 152 255 (SANKYO) * claim 1 *	1	
A,P	EP-A-0 210 545 (MERCK + CO.) * claim 1 *	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 K 5/06
C 07 F 9/30
C 07 F 9/32
C 07 F 9/65
A 61 K 37/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	07-03-1988	KAPTEYN H G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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